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(54) Title: RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

(57) Abstract: The present invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with respiratory and pulmonary disease, such as severe acute respiratory syndrome (SARS) virus genes, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful for modulating the expression and activity of SARS virus genes, or other genes involved in pathways of SARS virus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of SARS virus RNA.

RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

This application claims the benefit of U.S. Provisional Application No. 60/462,874, filed April 15, 2003, and is a continuation-in-part of U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003. This application is also a continuation-in-part of US Patent Application No. 10/427,160, filed April 30, 2003.

Reference is made to International Patent Application No. PCT/US03/05346, filed February 20, 2003, and International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of U.S. Provisional Application No. 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124 filed March 11, 2002, U.S. Provisional Application No. 60/386,782 filed June 6, 2002, U.S. Provisional Application No. 60/406,784 filed August 29, 2002, U.S. Provisional Application No. 60/408,378 filed September 5, 2002, U.S. Provisional Application No. 60/409,293 filed September 9, 2002, and U.S. Provisional Application No. 60/440,129 filed January 15, 2003. Reference is also made to International Patent Application No. PCT/US02/15876 filed May 17, 2002.

All the listed applications are hereby incorporated by reference herein in their entireties, including the drawings.

Field Of The Invention

The present invention concerns compounds, compositions, and methods for the study, diagnosis, and treatment of diseases and conditions that respond to the modulation of severe acute respiratory syndrome (SARS) associated cornavirus (SARS virus) gene expression and/or activity. The present invention also concerns compounds, compositions, and methods relating to conditions and diseases that respond to the modulation of expression and/or activity of genes involved in SARS virus pathways of

gene expression, including cellular genes that are involved in SARS virus infection. Specifically, the invention comprises small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of mediating RNA interference (RNAi) against severe acute respiratory syndrome (SARS) associated cornavirus gene expression.

Background Of The Invention

The following is a discussion of relevant art pertaining to RNAi. The discussion is provided only for understanding of the invention that follows. The summary is not an admission that any of the work described below is prior art to the claimed invention.

RNA interference refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, Cell, 101, 25-33; Fire *et al.*, 1998, *Nature*, 391, 806; Hamilton *et al.*, 1999, *Science*, 286, 950-951; Lin *et al.*, 1999, *Nature*, 402, 128-129; Sharp, 1999, Genes & Dev., 13:139-141; and Strauss, 1999, *Science*, 286, 886). The corresponding process in plants (Heifetz *et al.*, International PCT Publication No. WO 99/61631) is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes and is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from other known mechanisms involving double stranded RNA-specific ribonucleases, such as the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L (see for example US Patent Nos.

6,107,094; 5,898,031; Clemens *et al.*, 1997, *J. Interferon & Cytokine Res.*, 17, 503-524; Adah *et al.*, 2001, *Curr. Med. Chem.*, 8, 1189).

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer (Bass, 2000, Cell, 101, 235; Zamore *et al.*, 2000, Cell, 101, 25-33; Hammond *et al.*, 2000, Nature, 404, 293). Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, Cell, 101, 25-33; Bass, 2000, Cell, 101, 235; Berstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes (Zamore *et al.*, 2000, Cell, 101, 25-33; Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). Dicer has also been implicated in the excision of 21 and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188).

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Bahramian and Zarbl, 1999, *Molecular and Cellular Biology*, 19, 274-283 and Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mammalian systems. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494 and Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in Drosophila embryonic lysates (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide

overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with 2'-deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end of the guide sequence (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell*, 107, 309).

Studies have shown that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two-nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with deoxyribonucleotides has been reported to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164). In addition, Elbashir *et al.*, *supra*, also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.*, International PCT Publication No. WO 00/44914, and Beach *et al.*, International PCT Publication No. WO 01/68836 preliminarily suggest that siRNA may include modifications to either the phosphate-sugar backbone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom, however, neither application postulates to what extent such modifications would be tolerated in siRNA molecules, nor provides any further guidance or examples of such modified siRNA. Kreutzer *et al.*, Canadian Patent Application No. 2,359,180, also describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer *et al.* similarly fails to provide examples or guidance as to what extent these modifications would be tolerated in dsRNA molecules.

Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, tested certain chemical modifications targeting the unc-22 gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3 RNA polymerase and observed that RNAs with two phosphorothioate modified bases also had substantial decreases in effectiveness as RNAi. Further, Parrish *et al.* reported that phosphorothioate modification of more than two residues greatly destabilized the RNAs *in vitro* such that interference activities could not be assayed. *Id.* at 1081. The authors also tested certain modifications at the 2'-position of the nucleotide sugar in the long siRNA transcripts and found that substituting deoxynucleotides for ribonucleotides produced a substantial decrease in interference activity, especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. *Id.* In addition, the authors tested certain base modifications, including substituting, in sense and antisense strands of the siRNA, 4-thiouracil, 5-bromouracil, 5-iodouracil, and 3-(aminoallyl)uracil for uracil, and inosine for guanosine. Whereas 4-thiouracil and 5-bromouracil substitution appeared to be tolerated, Parrish reported that inosine produced a substantial decrease in interference activity when incorporated in either strand. Parrish also reported that incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in a substantial decrease in RNAi activity as well.

The use of longer dsRNA has been described. For example, Beach *et al.*, International PCT Publication No. WO 01/68836, describes specific methods for attenuating gene expression using endogenously-derived dsRNA. Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe a *Drosophila in vitro* RNAi system and the use of specific siRNA molecules for certain functional genomic and certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due to the danger of activating interferon response. Li *et al.*, International PCT Publication No. WO 00/44914, describe the use of specific long (141 bp-488 bp) enzymatically synthesized or vector expressed dsRNAs for attenuating the expression of certain target genes. Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646, describe certain methods for inhibiting the expression of particular genes in mammalian cells using certain long (550 bp-714 bp), enzymatically synthesized or vector expressed dsRNA

molecules. Fire *et al.*, International PCT Publication No. WO 99/32619, describe particular methods for introducing certain long dsRNA molecules into cells for use in inhibiting gene expression in nematodes. Plaetinck *et al.*, International PCT Publication No. WO 00/01846, describe certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific long dsRNA molecules. Mello *et al.*, International PCT Publication No. WO 01/29058, describe the identification of specific genes involved in dsRNA-mediated RNAi. Pachuck et al., International PCT Publication No. WO 00/63364, describe certain long (at least 200 nucleotide) dsRNA constructs. Deschamps Depaillette *et al.*, International PCT Publication No. WO 99/07409, describe specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Waterhouse *et al.*, International PCT Publication No. 99/53050 and 1998, *PNAS*, 95, 13959-13964, describe certain methods for decreasing the phenotypic expression of a nucleic acid in plant cells using certain dsRNAs. Driscoll *et al.*, International PCT Publication No. WO 01/49844, describe specific DNA expression constructs for use in facilitating gene silencing in targeted organisms.

Others have reported on various RNAi and gene-silencing systems. For example, Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, describe specific chemically-modified dsRNA constructs targeting the unc-22 gene of *C. elegans*. Grossniklaus, International PCT Publication No. WO 01/38551, describes certain methods for regulating polycomb gene expression in plants using certain dsRNAs. Churikov *et al.*, International PCT Publication No. WO 01/42443, describe certain methods for modifying genetic characteristics of an organism using certain dsRNAs. Cogoni *et al.*, International PCT Publication No. WO 01/53475, describe certain methods for isolating a Neurospora silencing gene and uses thereof. Reed *et al.*, International PCT Publication No. WO 01/68836, describe certain methods for gene silencing in plants. Honer *et al.*, International PCT Publication No. WO 01/70944, describe certain methods of drug screening using transgenic nematodes as Parkinson's Disease models using certain dsRNAs. Deak *et al.*, International PCT Publication No. WO 01/72774, describe certain *Drosophila*-derived gene products that may be related to RNAi in *Drosophila*. Arndt *et al.*, International PCT Publication No. WO 01/92513 describe certain methods for mediating gene suppression by using factors that enhance RNAi. Tuschl *et al.*,

International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs. Pachuk *et al.*, International PCT Publication No. WO 00/63364, and Satishchandran *et al.*, International PCT Publication No. WO 01/04313, describe certain methods and compositions for inhibiting the function of certain polynucleotide sequences using certain long (over 250 bp), vector expressed dsRNAs. Echeverri *et al.*, International PCT Publication No. WO 02/38805, describe certain *C. elegans* genes identified via RNAi. Kreutzer *et al.* International PCT Publications Nos. WO 02/055692, WO 02/055693, and EP 1144623 B1 describes certain methods for inhibiting gene expression using dsRNA. Graham *et al.*, International PCT Publications Nos. WO 99/49029 and WO 01/70949, and AU 4037501 describe certain vector expressed siRNA molecules. Fire *et al.*, US 6,506,559, describe certain methods for inhibiting gene expression in vitro using certain long dsRNA (299 bp-1033 bp) constructs that mediate RNAi. Martinez *et al.*, 2002, *Cell*, 110, 563-574, describe certain single stranded siRNA constructs, including certain 5'-phosphorylated single stranded siRNAs that mediate RNA interference in Hela cells. Harborth *et al.*, 2003, Antisense & Nucleic Acid Drug Development, 13, 83-105, describe certain chemically and structurally modified siRNA molecules. Chiu and Rana, 2003, RNA, 9, 1034-1048, describe certain chemically and structurally modified siRNA molecules.

McCaffrey *et al.*, 2002, *Nature*, 418, 38-39, describes the use of certain siRNA constructs targeting a chimeric SARS NS5B protein/luciferase transcript in mice.

Randall *et al.*, 2003, *PNAS USA*, 100, 235-240, describe certain siRNA constructs targeting SARS RNA in Huh7 hepatoma cell lines.

SUMMARY OF THE INVENTION

This invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with the development or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and/or other disease states associated with SARS virus infection,, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful

for modulating the expression and activity of severe acute respiratory syndrome (SARS) associated cornavirus or genes involved in severe acute respiratory syndrome (SARS) associated cornavirus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of severe acute respiratory syndrome (SARS) associated cornavirus. For convenience, all forms of the small nucleic acid molecules of the invention (*e.g.*, siRNA, dsRNA, micro-RNA, etc.) are referred to herein as "siNA," unless expressly stated otherwise.

A siNA of the invention can be unmodified or chemically-modified. A siNA of the instant invention can be chemically synthesized, expressed from a vector or enzymatically synthesized. The instant invention also features various chemically-modified synthetic short interfering nucleic acid (siNA) molecules capable of modulating repeat expansion gene expression or activity in cells by RNA interference (RNAi). The use of chemically-modified siNA improves various properties of native siNA molecules through increased resistance to nuclease degradation *in vivo* and/or through improved cellular uptake. Further, contrary to earlier published studies, siNA having multiple chemical modifications retains its RNAi activity. The siNA molecules of the instant invention are useful reagents and are useful in methods for a variety of therapeutic, diagnostic, target validation, genomic discovery, genetic engineering, and pharmacogenomic applications.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus. Specifically, the present invention comprises siNA molecules that modulate the expression of SARS proteins, for example, proteins encoded by SARS virus genome, such as Genbank Accession Nos. in Table I.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of genes representing cellular targets for SARS virus infection, such as cellular receptors,

cell surface molecules, cellular enzymes, cellular transcription factors, and/or cytokines, second messengers, and cellular accessory molecules.

Due to the high sequence variability of the SARS genome, selection of siNA molecules for broad therapeutic applications preferably involve the conserved regions of the SARS genome. In one embodiment, the present invention comprises siNA molecules that target the conserved regions of the SARS genome, such as the polymerase encoding region of the SARS virus genomic RNA. Therefore, siNA molecules of the invention are designed to target all the different isolates of SARS. siNA molecules designed to target conserved regions of various SARS isolates enable efficient inhibition of SARS replication in diverse patient populations and ensure the effectiveness of the siNA molecules against SARS quasi species that evolve due to mutations in the non-conserved regions of the SARS genome. Therefore, a single siNA molecule can be targeted against all isolates of SARS by designing the siNA molecule to interact with conserved nucleotide sequences of SARS (such conserved sequences are expected to be present in the RNA of all SARS isolates).

In one embodiment, a siNA molecule is designed to target the 3'-untranslated region and/or the shared leader sequence of genomic SARS RNA transcripts. Because SARS cornavirus mRNAs are nested with the genomic RNA and share common 3' region and polyA region, a single siNA targeting the 3'-end can target all transcripts plus the genomic RNA.

In one embodiment, a siNA molecule of the invention targets both the plus (genomic) strand RNA and minus strand RNA of the SARS virus. Because the SARS virus generates a minus strand RNA from plus strand genomic RNA, a double stranded siNA molecule targeting the plus strand will also target the minus strand, thus allowing a single double-stranded siNA to target both the plus (genomic) and the minus strand of the SARS virus. For example, a double stranded siNA molecule targeting the 3'-end of the SARS virus genomic strand will also target the 3'-end of the the minus strand, thus allowing a single double-stranded siNA to target both the plus and the minus strand of the SARS virus.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus and/or cellular proteins associated with the maintenance or development of SARS virus infection and/or acute respiratory failure, viral pneumonia, such as genes encoding sequences comprising those sequences referred to by GenBank Accession Nos. shown in **Table I**, referred to herein generally as SARS. The description below of the various aspects and embodiments of the invention is provided with reference to exemplary severe acute respiratory syndrome (SARS) associated cornavirus genes, generally referred to herein as SARS. However, such reference is meant to be exemplary only and the various aspects and embodiments of the invention are also directed to other genes that express alternate SARS genes, such as mutant SARS genes, splice variants of SARS genes, and genes encoding different strains of SARS, as well as as cellular targets for SARS, such as those described herein. The various aspects and embodiments are also directed to other genes involved in SARS pathways, including genes that encode cellular proteins involved in the maintenance and/or development of SARS virus infection and/or acute respiratory failure or other genes that express other proteins associated with SARS virus infection, such as cellular proteins that are utilized in the SARS life-cycle. Such additional genes can be analyzed for target sites using the methods described herein for SARS. Thus, the inhibition and the effects of such inhibition of the other genes can be performed as described herein. In other words, the term "SARS" as it is defined herein below and recited in the described embodiments, is meant to encompass genes associated with the development or maintenance of SARS virus infection, such as genes which encode SARS polypeptides, including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as cellular genes involved in SARS pathways of gene expression, replication, and/or SARS activity. Also, the term "SARS" as it is defined herein and recited in the described embodiments, is meant to encompass SARS viral gene products and cellular gene products involved in SARS virus infection, such as those described herein. Thus, each of the embodiments described herein with reference to the term "SARS" are applicable to all of the virus, cellular and viral protein, peptide, polypeptide, and/or polynucleotide molecules covered by the term "SARS" as that term is defined herein.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a severe acute respiratory syndrome virus (e.g., SARS) gene, wherein said siNA molecule comprises about 19 to about 23 base pairs. Preferably the number of based pairs in the siNA molecule is 18, 19, 20, 21, 22, 23, or 24.

In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS encoding sequence. In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS non-coding sequence or regulatory elements involved in SARS gene expression.

In one embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having SARS encoding sequence, such as those sequences having GenBank Accession Nos. shown in **Table I**. In another embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having other SARS encoding sequence, for example other mutant SARS genes not shown in **Table I** but known in the art to be associated with respiratory and/or pulmonary disease, SARS virus infection and/or acute respiratory failure, viral pneumonia, impeded respiration, respiratory distress syndrome, pulmonary hypertension, or pulmonary vasoconstriction. Chemical modifications as shown in **Tables III and IV** or otherwise described herein can be applied to any siNA construct of the invention. In another embodiment, a siNA molecule of the invention includes nucleotide sequence that can interact with nucleotide sequence of a SARS gene and thereby mediate silencing of SARS gene expression, for example, wherein the siNA mediates regulation of SARS gene expression by cellular processes that modulate the chromatin structure of the SARS gene and prevent transcription of the SARS gene.

In another embodiment, the invention features a siNA molecule comprising nucleotide sequence, for example, nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of

a SARS gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a SARS gene sequence or a portion thereof.

In one embodiment, the antisense region of SARS siNA constructs can comprise a sequence complementary to sequence having any of SEQ ID NOs. 1-1651 or 3303-3318. In one embodiment, the antisense region can also comprise sequence having any of SEQ ID NOs. 1652-3302, 3319-3326, 3335-3342, 3351-3358, 3367-3374, 3376, 3378, 3380, 3383, 3385, 3387, 3389, or 3392. In another embodiment, the sense region of the SARS constructs can comprise sequence having any of SEQ ID NOs. 1-1651, 3303-3310, 3311-3318, 3327-3334, 3343-3350, 3359-3366, 3375, 3377, 3379, 3381, 3382, 3384, 3386, 3388, 3390, or 3391.

In one embodiment, a siNA molecule of the invention comprises any of SEQ ID NOs. 1-3392. The sequences shown in SEQ ID NOs: 1-3392 are not limiting. A siNA molecule of the invention can comprise any contiguous SARS sequence (e.g., about 19 to about 25, or about 19, 20, 21, 22, 23, 24 or 25 contiguous SARS nucleotides).

In yet another embodiment, the invention features a siNA molecule comprising a sequence, for example, the antisense sequence of the siNA construct, complementary to a sequence or portion of sequence comprising sequence represented by GenBank Accession Nos. shown in **Table I**. Chemical modifications in **Tables III and IV** and described herein can be applied to any siNA construct of the invention. siNA molecules of the invention are unmodified or have up to all nucleotides modified with modifications according to Tables III and IV.

In one embodiment of the invention a siNA molecule comprises an antisense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense strand is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, and wherein said sense strand and said antisense strand are distinct nucleotide sequences with at least about 19 complementary nucleotides.

In another embodiment of the invention a siNA molecule of the invention comprises an antisense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense region is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein said sense region and said antisense region comprise a linear molecule with at least about 19 complementary nucleotides.

In one embodiment of the invention a siNA molecule comprises an antisense strand comprising a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof encoding a SARS protein. The siNA further comprises a sense strand, wherein said sense strand comprises a nucleotide sequence of a SARS gene or a portion thereof.

In another embodiment, a siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence encoding a SARS protein or a portion thereof. The siNA molecule further comprises a sense region, wherein said sense region comprises a nucleotide sequence of a SARS gene or a portion thereof.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a SARS gene. Because SARS genes can share some degree of sequence homology with each other, siNA molecules can be designed to target a class of SARS genes or alternately specific SARS genes by selecting sequences that are either shared among different SARS targets (e.g., differnet viral strains) or alternatively that are unique for a specific SARS target (e.g., a particular viral strain). Therefore, in one embodiment, the siNA molecule can be designed to target conserved regions of SARS RNA sequences having homology among several SARS genes so as to target several SARS genes (e.g., different SARS isoforms, splice variants, mutant genes etc.) with one siNA molecule. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific SARS RNA sequence due to the high degree of specificity that the siNA molecule requires to mediate RNAi activity.

In one embodiment, nucleic acid molecules of the invention that act as mediators of the RNA interference gene silencing response are double-stranded nucleic acid molecules. In another embodiment, the siNA molecules of the invention consist of duplexes containing about 19 base pairs between oligonucleotides comprising about 19 to about 25 (*e.g.*, 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides. In yet another embodiment, siNA molecules of the invention comprise duplexes with overhanging ends of about about 1 to about 3 (*e.g.*, 1, 2, 3, or 4) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3'-terminal mononucleotide, dinucleotide, or trinucleotide overhangs.

In one embodiment, the invention features one or more chemically-modified siNA constructs having specificity for SARS expressing nucleic acid molecules, such as RNA encoding a SARS protein. Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides, "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and/or inverted deoxy abasic residue incorporation. These chemical modifications, when used in various siNA constructs, are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds. Furthermore, contrary to the data published by Parrish *et al., supra,* applicant demonstrates that multiple (greater than one) phosphorothioate substitutions are well-tolerated and confer substantial increases in serum stability for modified siNA constructs.

In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides can be used to improve *in vitro* or *in vivo* characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA

molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

One aspect of the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene. In one embodiment, a double stranded siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 21 nucleotides long. In one embodiment, the double-stranded siNA molecule does not contain any ribonucleotides. In another embodiment, the double-stranded siNA molecule comprises one or more ribonucleotides. In one embodiment, each strand of the double-stranded siNA molecule comprises about 19 to about 23 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides, wherein each strand comprises about 19 nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof of the SARS gene, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of the SARS gene or a portion thereof, and a sense region, wherein the sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In one embodiment, the antisense region and the sense region each comprise about 19 to about 23 (e.g. about 19, 20, 21, 22, or 23) nucleotides, wherein the antisense region comprises about 19 nucleotides that are complementary to nucleotides of the sense region.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region.

In one embodiment, the SARS virus RNA comtemplated by the invention comprises SARS virus minus strand RNA. In another embodiment, the SARS virus RNA comtemplated by the invention comprises SARS virus plus strand RNA.

In one embodiment, a siNA molecule of the invention comprises blunt ends, i.e., ends that do not include any overhanging nucleotides. For example, a siNA molecule of the invention comprising modifications described herein (e.g., comprising nucleotides having Formulae I-VII or siNA constructs comprising Stab00-Stab22 or any combination thereof (see **Table IV**)) and/or any length described herein can comprise blunt ends or ends with no overhanging nucleotides.

In one embodiment, any siNA molecule of the invention can comprise one or more blunt ends, i.e., where a blunt end does not have any overhanging nucleotides. In a non-limiting example, a blunt ended siNA molecule has a number of base pairs equal to the number of nucleotides present in each strand of the siNA molecule. In another example, a siNA molecule comprises one blunt end, for example wherein the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises one blunt end, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises two blunt ends, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand as well as the 5'-end of the antisense strand and 3'-end of the sense strand do not have any overhanging nucleotides. A blunt ended siNA molecule can comprise, for example, from about 18 to about 30 nucleotides (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides). Other nucleotides present in a blunt ended siNA molecule can comprise mismatches, bulges, loops, or wobble base pairs, for example, to modulate the activity of the siNA molecule to mediate RNA interference.

By "blunt ends" is meant symmetric termini or termini of a double stranded siNA molecule having no overhanging nucleotides. The two strands of a double stranded siNA molecule align with each other without over-hanging nucleotides at the termini. For example, a blunt ended siNA construct comprises terminal nucleotides that are complementary between the sense and antisense regions of the siNA molecule.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. The sense region can be connected to the antisense region via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker.

In one embodiment, the invention features double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule comprises about 19 to about 21 base pairs, and wherein each strand of the siNA molecule comprises one or more chemical modifications. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises no ribonucleotides. In another embodiment, a siNA molecule of the invention comprises ribonucleotides.

In one embodiment, a siNA molecule of the invention comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the siNA further comprises a sense region comprising a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In another embodiment, the antisense region and the sense region each comprise about 19 to about 23 nucleotides and the antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS gene, or a portion thereof, and the sense region comprises a nucleotide sequence that is complementary to the antisense region. In another embodiment, the siNA molecule is assembled from two separate oligonucleotide fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule, such as a nucleotide or non-nucleotide linker. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the siNA molecule has one or more modified pyrimidine and/or purine nucleotides. In one embodiment, the pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine

nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In one embodiment, the pyrimidine nucleotides in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the antisense region are 2'-O-methyl or 2'-deoxy purine nucleotides. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the sense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule, and wherein the fragment comprising the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment. In another embodiment, the terminal cap moiety is an inverted deoxy abasic moiety or glyceryl moiety. In another embodiment, each of the two fragments of the siNA molecule comprise about 21 nucleotides.

In one embodiment, the invention features a siNA molecule comprising at least one modified nucleotide, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. The siNA can be, for example, of length between about 12 and about 36 nucleotides. In another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-

deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a method of increasing the stability of a siNA molecule against cleavage by ribonucleases comprising introducing at least one modified nucleotide into the siNA molecule, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. In another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a

nucleotide sequence that is complementary to the antisense region, and wherein the purine nucleotides present in the antisense region comprise 2'-deoxy- purine nucleotides. In an alternative embodiment, the purine nucleotides present in the antisense region comprise 2'-O-methyl purine nucleotides. In either of the above embodiments, the antisense region can comprise a phosphorothioate internucleotide linkage at the 3' end of the antisense region. Alternatively, in either of the above embodiments, the antisense region can comprise a glyceryl modification at the 3' end of the antisense region. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the antisense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the antisense region of a siNA molecule of the invention comprises sequence complementary to a portion of a SARS transcript having sequence unique to a particular SARS disease related allele, such as sequence comprising a SNP associated with the disease specific allele. As such, the antisense region of a siNA molecule of the invention can comprise sequence complementary to sequences that are unique to a particular allele to provide specificity in mediating selective RNAi against the disease related allele.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the

RNA encoded by the SARS gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the SARS gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a SARS RNA sequence (e.g., wherein said target RNA sequence is encoded by a SARS gene involved in the SARS pathway), wherein the siNA molecule does not contain any ribonucleotides and wherein each strand of the double-stranded siNA molecule is about 21 nucleotides long. Examples of non-ribonucleotide containing siNA constructs are combinations of stabilization chemistries shown in Table IV in any combination of Sense/Antisense chemistries, such as Stab 7/8, Stab 7/11, Stab 8/8, Stab 18/8, Stab 18/11, Stab 12/13, Stab 7/13, Stab 18/13, Stab 7/19, Stab 8/19, Stab 18/19, Stab 7/20, Stab 8/20, or Stab 18/20.

In one embodiment, the invention features a chemically synthesized double stranded RNA molecule that directs cleavage of a SARS RNA via RNA interference, wherein each strand of said RNA molecule is about 21 to about 23 nucleotides in length; one strand of the RNA molecule comprises nucleotide sequence having sufficient complementarity to the SARS RNA for the RNA molecule to direct cleavage of the SARS RNA via RNA interference; and wherein at least one strand of the RNA molecule comprises one or more chemically modified nucleotides described herein, such as deoxynucleotides, 2'-O-methyl nucleotides, 2'-deoxy-2'-fluoro nucloetides, 2'-O-methoxyethyl nucleotides etc.

In one embodiment, the invention features a medicament comprising a siNA molecule of the invention.

In one embodiment, the invention features an active ingredient comprising a siNA molecule of the invention.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule to down-regulate expression of a SARS gene,

wherein the siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 18 to about 28 or more (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or more) nucleotides long.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA that encodes a protein or portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other

strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, each strand of the siNA molecule comprises about 18 to about 29 or more (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein each strand comprises at least about 18 nucleotides that are complementary to the nucleotides of the other strand. In another embodiment, the siNA molecule is assembled from two oligonucleotide fragments, wherein one fragment comprises the nucleotide sequence of the antisense strand of the siNA molecule and a second fragment comprises nucleotide sequence of the sense region of the siNA molecule. In yet another embodiment, the sense strand is connected to the antisense strand via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker. In a further embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In still another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides. In another embodiment, the antisense strand comprises one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides and one or more 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides. In a further embodiment the sense strand comprises a 3'-end and a 5'-end, wherein a terminal cap moiety (e.g., an inverted deoxy abasic moiety or inverted deoxy nucleotide moiety such as inverted thymidine) is present at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In another embodiment, the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand. In another embodiment, the antisense strand comprises a glyceryl modification at the 3' end. In another embodiment, the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein each of the two strands of the siNA molecule comprises about 21 nucleotides. In one embodiment, about 21 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule, wherein at least two 3' terminal nucleotides of each strand of the siNA molecule are not base-paired to the nucleotides of the other strand of the siNA molecule. In another embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine, such as 2'-deoxy-thymidine. In another embodiment, each strand of the siNA molecule is base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof. In another embodiment, about 21 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence or a portion thereof of the antisense strand is complementary to a nucleotide sequence of the untranslated region or a portion thereof of the SARS RNA.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence of the SARS RNA or a portion thereof that is present in the SARS RNA.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention in a pharmaceutically acceptable carrier or diluent.

In a non-limiting example, the introduction of chemically-modified nucleotides into nucleic acid molecules provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules that are delivered exogenously. For example, the use of chemically-modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically-modified nucleic acid molecules tend to have a longer half-life in serum. Furthermore, certain chemical modifications can improve the bioavailability of nucleic acid molecules by targeting particular cells or tissues and/or improving cellular uptake of the nucleic acid molecule. Therefore, even if the activity of

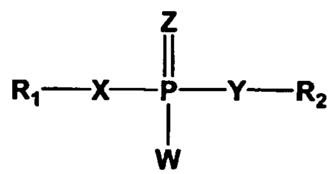
a chemically-modified nucleic acid molecule is reduced as compared to a native nucleic acid molecule, for example, when compared to an all-RNA nucleic acid molecule, the overall activity of the modified nucleic acid molecule can be greater than that of the native molecule due to improved stability and/or delivery of the molecule. Unlike native unmodified siNA, chemically-modified siNA can also minimize the possibility of activating interferon activity in humans.

In any of the embodiments of siNA molecules described herein, the antisense region of a siNA molecule of the invention can comprise a phosphorothioate internucleotide linkage at the 3'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the antisense region can comprise about one to about five phosphorothioate internucleotide linkages at the 5'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs of a siNA molecule of the invention can comprise ribonucleotides or deoxyribonucleotides that are chemically-modified at a nucleic acid sugar, base, or backbone. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more universal base ribonucleotides. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more acyclic nucleotides.

One embodiment of the invention provides an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention in a manner that allows expression of the nucleic acid molecule. Another embodiment of the invention provides a mammalian cell comprising such an expression vector. The mammalian cell can be a human cell. The siNA molecule of the expression vector can comprise a sense region and an antisense region. The antisense region can comprise sequence complementary to a RNA or DNA sequence encoding SARS and the sense region can comprise sequence complementary to the antisense region. The siNA molecule can comprise two distinct strands having complementary sense and antisense regions. The siNA molecule can comprise a single strand having complementary sense and antisense regions.

In one embodiment, the nucleotide sequence of the antisense strand or a portion thereof of a siNA molecule of the invention is complementary to the nucleotide sequence of a SARS RNA or a portion thereof that is present in the RNA of all SARS isolates.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides comprising a backbone modified internucleotide linkage having Formula I:

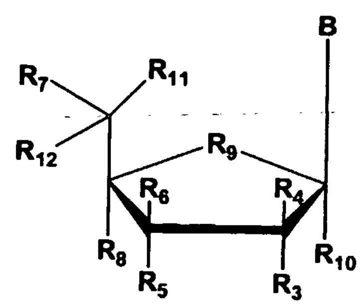


wherein each R1 and R2 is independently any nucleotide, non-nucleotide, or polynucleotide which can be naturally-occurring or chemically-modified, each X and Y is independently O, S, N, alkyl, or substituted alkyl, each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, or acetyl and wherein W, X, Y, and Z are optionally not all O. In another embodiment, a backbone modification of the invention comprises a phosphonoacetate and/or thiophosphonoacetate internucleotide linkage (see for example Sheehan et al., 2003, Nucleic Acids Research, 31, 4109-4118).

The chemically-modified internucleotide linkages having Formula I, for example, wherein any Z, W, X, and/or Y independently comprises a sulphur atom, can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) chemically-modified internucleotide linkages having Formula I at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified internucleotide linkages having Formula I at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine

nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In another embodiment, a siNA molecule of the invention having internucleotide linkage(s) of Formula I also comprises a chemically-modified nucleotide or non-nucleotide having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula II:

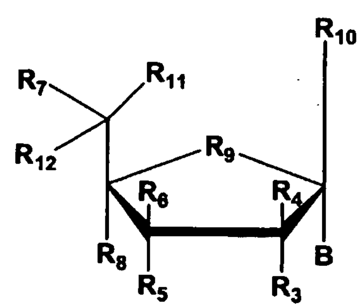


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine,

pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula II can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula II at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 5'-end of the sense strand, the antisense strand, or both strands. In anther non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end of the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula III:



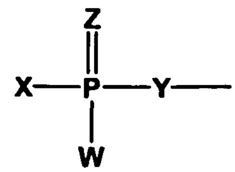
wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-

aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be employed to be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula III can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide(s) or non-nucleotide(s) of Formula III at the 5'-end of the sense strand, the antisense strand, or both strands. In anther non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end of the sense strand, the antisense strand, or both strands.

In another embodiment, a siNA molecule of the invention comprises a nucleotide having Formula II or III, wherein the nucleotide having Formula II or III is in an inverted configuration. For example, the nucleotide having Formula II or III is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a 5'-terminal phosphate group having Formula IV:



wherein each X and Y is independently O, S, N, alkyl, substituted alkyl, or alkylhalo; wherein each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, alkylhalo, or acetyl; and wherein W, X, Y and Z are not all O.

In one embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand, for example, a strand complementary to a target RNA, wherein the siNA molecule comprises an all RNA siNA molecule. In another embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand wherein the siNA molecule also comprises about 1 to about 3 (*e.g.*, about 1, 2, or 3) nucleotide 3'-terminal nucleotide overhangs having about 1 to about 4 (*e.g.*, about 1, 2, 3, or 4) deoxyribonucleotides on the 3'-end of one or both strands. In another embodiment, a 5'-terminal phosphate group having Formula IV is present on the target-complementary strand of a siNA molecule of the invention, for example a siNA molecule having chemical modifications having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more phosphorothioate internucleotide linkages. For example, in a non-limiting example, the invention features a chemically-modified short interfering nucleic acid (siNA) having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in one siNA strand. In yet another embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) individually having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in both siNA strands. The phosphorothioate internucleotide linkages can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both of the 3'- and

5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the sense strand comprises about 1 to about 5, specifically about 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) 2'-deoxy,

2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5 or more, for example about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a siNA molecule, wherein the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more

phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule having about 1 to about 5, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages in each strand of the siNA molecule.

In another embodiment, the invention features a siNA molecule comprising 2'-5' internucleotide linkages. The 2'-5' internucleotide linkage(s) can be at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both siNA sequence strands. In addition, the 2'-5' internucleotide linkage(s) can be present at various other positions within one or both siNA sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage.

In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27 (*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length, wherein the duplex has about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII. For example, an exemplary chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein each strand consists of about 21 nucleotides, each having a 2-nucleotide 3'-terminal nucleotide overhang, and wherein the duplex has about 19 base pairs. In another embodiment, a siNA molecule of the invention comprises a single stranded hairpin structure, wherein the siNA is about 36 to about 70 (*e.g.*, about 36, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 19 base pairs and a 2-nucleotide 3'-terminal nucleotide overhang. In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. For example, a linear hairpin siNA molecule of the invention is designed such that degradation of the loop portion of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In another embodiment, a siNA molecule of the invention comprises a hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31,

32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 3 to about 23 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another embodiment, a linear hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 20 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms an asymmetric hairpin structure having about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, an asymmetric hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is

biodegradable. In another embodiment, an asymmetric hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

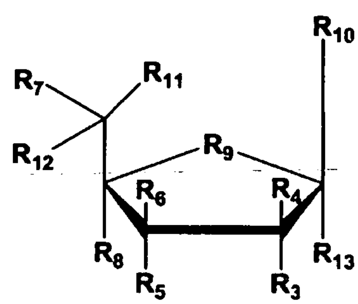
In another embodiment, a siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 16 to about 25 (*e.g.*, about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides in length, wherein the sense region is about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 18 to about 22 (*e.g.*, about 18, 19, 20, 21, or 22) nucleotides in length and wherein the sense region is about 3 to about 15 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) nucleotides in length, wherein the sense region the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. In another embodiment, the asymmetic double stranded siNA molecule can also have a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV).

In another embodiment, a siNA molecule of the invention comprises a circular nucleic acid molecule, wherein the siNA is about 38 to about 70 (*e.g.*, about 38, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification, which comprises a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a circular oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof,

wherein the circular oligonucleotide forms a dumbbell shaped structure having about 19 base pairs and 2 loops.

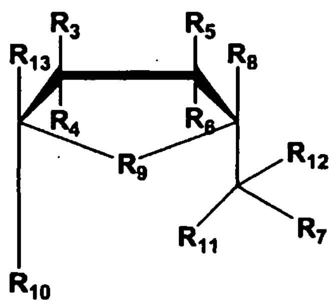
In another embodiment, a circular siNA molecule of the invention contains two loop motifs, wherein one or both loop portions of the siNA molecule is biodegradable. For example, a circular siNA molecule of the invention is designed such that degradation of the loop portions of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) abasic moiety, for example a compound having Formula V:



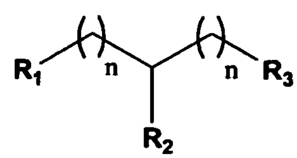
wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2.

In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) inverted abasic moiety, for example a compound having Formula VI:



wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and either R2, R3, R8 or R13 serve as points of attachment to the siNA molecule of the invention.

In another embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) substituted polyalkyl moieties, for example a compound having Formula VII:



wherein each n is independently an integer from 1 to 12, each R1, R2 and R3 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or a group having Formula I, and R1, R2 or R3 serves as points of attachment to the siNA molecule of the invention.

In another embodiment, the invention features a compound having Formula VII, wherein R1 and R2 are hydroxyl (OH) groups, n = 1, and R3 comprises O and is the point of attachment to the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both strands of a double-stranded siNA molecule of the invention or to a single-stranded siNA molecule of the invention. This modification is referred to herein as "glyceryl" (for example modification 6 in **Figure 10**).

In another embodiment, a moiety having any of Formula V, VI or VII of the invention is at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of a siNA molecule of the invention. For example, a moiety having Formula V, VI or VII can be present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand, the sense strand, or both antisense and sense strands of the siNA molecule. In addition, a moiety having Formula VII can be present at the 3'-end or the 5'-end of a hairpin siNA molecule as described herein.

In another embodiment, a siNA molecule of the invention comprises an abasic residue having Formula V or VI, wherein the abasic residue having Formula VI or VI is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid (LNA) nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In another embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-

2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine

nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said antisense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or

more or all) purine nucleotides present in the antisense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system comprising a sense region, wherein one or more pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and an antisense region, wherein one or more pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). The sense region and/or the antisense region can have a terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the

sense and/or antisense sequence. The sense and/or antisense region can optionally further comprise a 3'-terminal nucleotide overhang having about 1 to about 4 (e.g., about 1, 2, 3, or 4) 2'-deoxynucleotides. The overhang nucleotides can further comprise one or more (e.g., about 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages. Non-limiting examples of these chemically-modified siNAs are shown in **Figures 4 and 5** and **Tables III and IV** herein. In any of these described embodiments, the purine nucleotides present in the sense region are alternatively 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides) and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Also, in any of these embodiments, one or more purine nucleotides present in the sense region are alternatively purine ribonucleotides (e.g., wherein all purine nucleotides are purine ribonucleotides or alternately a plurality of purine nucleotides are purine ribonucleotides) and any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Additionally, in any of these embodiments, one or more purine nucleotides present in the sense region and/or present in the antisense region are alternatively selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides (e.g., wherein all purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides or alternately a plurality of purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides).

In another embodiment, any modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, comprise modified nucleotides having properties or characteristics similar to naturally occurring

ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, are resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi. Non-limiting examples of nucleotides having a northern configuration include locked nucleic acid (LNA) nucleotides (e.g., 2′-O, 4′-C-methylene-(D-ribofuranosyl) nucleotides); 2'-methoxyethoxy (MOE) nucleotides; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy-2'-chloro nucleotides, 2'-azido nucleotides, and 2'-O-methyl nucleotides.

In one embodiment, the sense strand of a double stranded siNA molecule of the invention comprises a terminal cap moiety, (see for example **Figure 10**) such as an inverted deoxyabaisc moiety, at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid molecule (siNA) capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a conjugate covalently attached to the chemically-modified siNA molecule. Non-limiting examples of conjugates contemplated by the invention include conjugates and ligands described in Vargeese *et al.*, USSN 10/427,160, filed April 30, 2003, incorporated by reference herein in its entirety, including the drawings. In another embodiment, the conjugate is covalently attached to the chemically-modified siNA molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In yet another embodiment, the conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule, or any

combination thereof. In one embodiment, a conjugate molecule of the invention comprises a molecule that facilitates delivery of a chemically-modified siNA molecule into a biological system, such as a cell. In another embodiment, the conjugate molecule attached to the chemically-modified siNA molecule is a polyethylene glycol, human serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to chemically-modified siNA molecules are described in Vargeese *et al.*, U.S. Serial No. 10/201,394, filed July 22, 2002, incorporated by reference herein. The type of conjugates used and the extent of conjugation of siNA molecules of the invention can be evaluated for improved pharmacokinetic profiles, bioavailability, and/or stability of siNA constructs while at the same time maintaining the ability of the siNA to mediate RNAi activity. As such, one skilled in the art can screen siNA constructs that are modified with various conjugates to determine whether the siNA conjugate complex possesses improved properties while maintaining the ability to mediate RNAi, for example in animal models as are generally known in the art.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule of the invention, wherein the siNA further comprises a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the siNA to the antisense region of the siNA. In one embodiment, a nucleotide linker of the invention can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those in the art will recognize that other embodiments can be readily generated using techniques generally known in the art. (See, for example, Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; Brody and Gold, 2000, *J. Biotechnol.*, 74, 5; Sun, 2000, *Curr. Opin.*

Mol. Ther., 2, 100; Kusser, 2000, *J. Biotechnol.*, 74, 27; Hermann and Patel, 2000, *Science*, 287, 820; and Jayasena, 1999, *Clinical Chemistry*, 45, 1628.)

In yet another embodiment, a non-nucleotide linker of the invention comprises abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds (e.g. polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, *18*:6353 and *Nucleic Acids Res.* 1987, *15*:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:5109; Ma *et al.*, *Nucleic Acids Res.* 1993, *21*:2585 and *Biochemistry* 1993, *32*:1751; Durand *et al.*, *Nucleic Acids Res.* 1990, *18*:6353; McCurdy *et al.*, *Nucleosides & Nucleotides* 1991, *10*:287; Jschke *et al.*, *Tetrahedron Lett.* 1993, *34*:301; Ono *et al.*, *Biochemistry* 1991, *30*:9914; Arnold *et al.*, International Publication No. WO 89/02439; Usman *et al.*, International Publication No. WO 95/06731; Dudycz *et al.*, International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, *113*:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine, for example at the C1 position of the sugar.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) inside a cell or reconstituted *in vitro* system, wherein one or both strands of the siNA molecule that are assembled from two separate oligonucleotides do not comprise any ribonucleotides. For example, a siNA molecule can be assembled from a single oligonculeotide where the sense and antisense regions of the siNA comprise separate oligonucleotides not having any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotides. In another example, a siNA molecule can be assembled from a single oligonculeotide where the sense and antisense regions of the siNA are linked or circularized by a nucleotide or non-nucleotide linker as desrcibed herein, wherein the oligonucleotide does not have any

ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotide. Applicant has surprisingly found that the presense of ribonucleotides (e.g., nucleotides having a 2'-hydroxyl group) within the siNA molecule is not required or essential to support RNAi activity. As such, in one embodiment, all positions within the siNA can include chemically modified nucleotides and/or non-nucleotides such as nucleotides and or non-nucleotides having Formula I, II, III, IV, V, VI, or VII or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group and a 3'-terminal phosphate group (e.g., a 2',3'-cyclic phosphate). In another embodiment, the single stranded siNA molecule of the invention comprises about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides. In yet another embodiment, the single stranded siNA molecule of the invention comprises one or more chemically modified nucleotides or non-nucleotides described herein. For example, all the positions within the siNA molecule can include chemically-modified nucleotides such as nucleotides having any of Formulae I-VII, or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro systemcomprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence, wherein one or more pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine

nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and a terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence. The siNA optionally further comprises about 1 to about 4 or more (e.g., about 1, 2, 3, 4 or more) terminal 2'-deoxynucleotides at the 3'-end of the siNA molecule, wherein the terminal nucleotides can further comprise one or more (e.g., 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages, and wherein the siNA optionally further comprises a terminal phosphate group, such as a 5'-terminal phosphate group. In any of these embodiments, any purine nucleotides present in the antisense region are alternatively 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA (i.e., purine nucleotides present in the sense and/or antisense region) can alternatively be locked nucleic acid (LNA) nucleotides (e.g., wherein all purine nucleotides are LNA nucleotides or alternately a plurality of purine nucleotides are LNA nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA are alternatively 2'-methoxyethyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-methoxyethyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-methoxyethyl purine nucleotides). In another embodiment, any modified nucleotides present in the single stranded siNA molecules of the invention comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the single stranded siNA molecules of the invention are preferably resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi.

In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the

siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

In another embodiment, the invention features a method for modulating the expression of two or more SARS genes within a cell comprising: (a) synthesizing one or more siNA molecules of the invention, which can be chemically-modified, wherein the siNA strands comprise sequences complementary to RNA of the SARS genes and wherein the sense strand sequences of the siNAs comprise sequences identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA

molecule into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, siNA molecules of the invention are used as reagents in *ex vivo* applications. For example, siNA reagents are intoduced into tissue or cells that are transplanted into a subject for therapeutic effect. The cells and/or tissue can be derived from an organism or subject that later receives the explant, or can be derived from another organism or subject prior to transplantation. The siNA molecules can be used to modulate the expression of one or more genes in the cells or tissue, such that the cells or tissue obtain a desired phenotype or are able to perform a function when transplanted in vivo. In one embodiment, certain target cells from a patient are extracted. These extracted cells are contacted with siNAs targeteing a specific nucleotide sequence within the cells under conditions suitable for uptake of the siNAs by these cells (e.g. using delivery reagents such as cationic lipids, liposomes and the like or using techniques such as electroporation to facilitate the delivery of siNAs into cells). The cells are then reintroduced back into the same patient or other patients. In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate

the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of the SARS gene in the organism. The level of SARS protein or RNA can be determined as is known in the art.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism. The level of SARS protein or RNA can be determined as is known in the art.

In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the

invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) contacting the cell in vitro or in vivo with the siNA molecule under conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) contacting the cell of the tissue explant derived from a particular organism with the siNA molecule under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising contacting the organism with a siNA molecule of the invention under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising contacting the organism with one or more siNA molecules of the invention under conditions suitable to modulate the expression of the SARS genes in the organism.

The siNA molecules of the invention can be designed to down regulate or inhibit target (e.g., SARS) gene expression through RNAi targeting of a variety of RNA molecules. In one embodiment, the siNA molecules of the invention are used to target various RNAs corresponding to a target gene. Non-limiting examples of such RNAs include messenger RNA (mRNA), alternate RNA splice variants of target gene(s), post-transcriptionally modified RNA of target gene(s), pre-mRNA of target gene(s), and/or RNA templates. If alternate splicing produces a family of transcripts that are distinguished by usage of appropriate exons, the instant invention can be used to inhibit gene expression through the appropriate exons to specifically inhibit or to distinguish among the functions of gene family members. For example, a protein that contains an

alternatively spliced transmembrane domain can be expressed in both membrane bound and secreted forms. Use of the invention to target the exon containing the transmembrane domain can be used to determine the functional consequences of pharmaceutical targeting of membrane bound as opposed to the secreted form of the protein. Non-limiting examples of applications of the invention relating to targeting these RNA molecules include therapeutic pharmaceutical applications, pharmaceutical discovery applications, molecular diagnostic and gene function applications, and gene mapping, for example using single nucleotide polymorphism mapping with siNA molecules of the invention. Such applications can be implemented using known gene sequences or from partial sequences available from an expressed sequence tag (EST).

In another embodiment, the siNA molecules of the invention are used to target conserved sequences corresponding to a gene family or gene families such as SARS family genes. As such, siNA molecules targeting multiple SARS targets can provide increased therapeutic effect. In addition, siNA can be used to characterize pathways of gene function in a variety of applications. For example, the present invention can be used to inhibit the activity of target gene(s) in a pathway to determine the function of uncharacterized gene(s) in gene function analysis, mRNA function analysis, or translational analysis. The invention can be used to determine potential target gene pathways involved in various diseases and conditions toward pharmaceutical development. The invention can be used to understand pathways of gene expression involved in, for example, the progression and/or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue.

In one embodiment, siNA molecule(s) and/or methods of the invention are used to down regulate the expression of gene(s) that encode RNA referred to by Genbank Accession, for example SARS genes encoding RNA sequence(s) referred to herein by Genbank Accession number, for example, Genbank Accession Nos. shown in **Table I**.

In one embodiment, the invention features a method comprising: (a) generating a library of siNA constructs having a predetermined complexity; and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RNA sequence. In one embodiment, the siNA molecules of (a) have strands of

a fixed length, for example, about 23 nucleotides in length. In another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (*e.g.*, about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In one embodiment, the invention features a method comprising: (a) generating a randomized library of siNA constructs having a predetermined complexity, such as of 4^N, where N represents the number of base paired nucleotides in each of the siNA construct strands (*eg.* for a siNA construct having 21 nucleotide sense and antisense strands with 19 base pairs, the complexity would be 4^{19}); and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target SARS RNA sequence. In another embodiment, the siNA molecules of (a) have strands of a fixed length, for example about 23 nucleotides in length. In yet another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (*e.g.*, about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described in Example 7 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of SARS RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target SARS RNA sequence. The target SARS RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In another embodiment, the invention features a method comprising: (a) analyzing the sequence of a RNA target encoded by a target gene; (b) synthesizing one or more sets

of siNA molecules having sequence complementary to one or more regions of the RNA of (a); and (c) assaying the siNA molecules of (b) under conditions suitable to determine RNAi targets within the target RNA sequence. In one embodiment, the siNA molecules of (b) have strands of a fixed length, for example about 23 nucleotides in length. In another embodiment, the siNA molecules of (b) are of differing length, for example having strands of about 19 to about 25 (*e.g.*, about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. Fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by expression in *in vivo* systems.

By "target site" is meant a sequence within a target RNA that is "targeted" for cleavage mediated by a siNA construct which contains sequences within its antisense region that are complementary to the target sequence.

By "detectable level of cleavage" is meant cleavage of target RNA (and formation of cleaved product RNAs) to an extent sufficient to discern cleavage products above the background of RNAs produced by random degradation of the target RNA. Production of cleavage products from 1-5% of the target RNA is sufficient to detect above the background for most methods of detection.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a method for diagnosing a disease or condition in a subject comprising administering to the subject a composition of the invention under conditions suitable for the diagnosis of the disease or condition in the subject. In another embodiment, the invention features a method for

treating or preventing a disease or condition in a subject, comprising administering to the subject a composition of the invention under conditions suitable for the treatment or prevention of the disease or condition in the subject, alone or in conjunction with one or more other therapeutic compounds. In yet another embodiment, the invention features a method for reducing or preventing tissue rejection in a subject comprising administering to the subject a composition of the invention under conditions suitable for the reduction or prevention of tissue rejection in the subject.

In another embodiment, the invention features a method for validating a SARS gene target, comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a cell, tissue, or organism under conditions suitable for modulating expression of the SARS target gene in the cell, tissue, or organism; and (c) determining the function of the gene by assaying for any phenotypic change in the cell, tissue, or organism.

In another embodiment, the invention features a method for validating a SARS target comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a biological system under conditions suitable for modulating expression of the SARS target gene in the biological system; and (c) determining the function of the gene by assaying for any phenotypic change in the biological system.

By "biological system" is meant, material, in a purified or unpurified form, from biological sources, including but not limited to human or animal, wherein the system comprises the components required for RNAi acitivity. The term "biological system" includes, for example, a cell, tissue, or organism, or extract thereof. The term biological system also includes reconstituted RNAi systems that can be used in an *in vitro* setting.

By "phenotypic change" is meant any detectable change to a cell that occurs in response to contact or treatment with a nucleic acid molecule of the invention (e.g., siNA). Such detectable changes include, but are not limited to, changes in shape, size, proliferation, motility, protein expression or RNA expression or other physical or

chemical changes as can be assayed by methods known in the art. The detectable change can also include expression of reporter genes/molecules such as Green Florescent Protein (GFP) or various tags that are used to identify an expressed protein or any other cellular component that can be assayed.

In one embodiment, the invention features a kit containing a siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of a SARS target gene in a biological system, including, for example, in a cell, tissue, or organism. In another embodiment, the invention features a kit containing more than one siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of more than one SARS target gene in a biological system, including, for example, in a cell, tissue, or organism.

In one embodiment, the invention features a cell containing one or more siNA molecules of the invention, which can be chemically-modified. In another embodiment, the cell containing a siNA molecule of the invention is a mammalian cell. In yet another embodiment, the cell containing a siNA molecule of the invention is a human cell.

In one embodiment, the synthesis of a siNA molecule of the invention, which can be chemically-modified, comprises: (a) synthesis of two complementary strands of the siNA molecule; (b) annealing the two complementary strands together under conditions suitable to obtain a double-stranded siNA molecule. In another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase oligonucleotide synthesis. In yet another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase tandem oligonucleotide synthesis.

In one embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing a first oligonucleotide sequence strand of the siNA molecule, wherein the first oligonucleotide sequence strand comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of the second oligonucleotide sequence strand of the siNA; (b) synthesizing the second oligonucleotide sequence strand of siNA on the scaffold of the first oligonucleotide sequence strand, wherein the second oligonucleotide sequence strand further comprises a chemical moiety than can be used to purify the siNA duplex; (c) cleaving the linker molecule of (a) under

conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex; and (d) purifying the siNA duplex utilizing the chemical moiety of the second oligonucleotide sequence strand. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions using an alkylamine base such as methylamine. In one embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place concomitantly. In another embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group, which can be employed in a trityl-on synthesis strategy as described herein. In yet another embodiment, the chemical moiety, such as a dimethoxytrityl group, is removed during purification, for example, using acidic conditions.

In a further embodiment, the method for siNA synthesis is a solution phase synthesis or hybrid phase synthesis wherein both strands of the siNA duplex are synthesized in tandem using a cleavable linker attached to the first sequence which acts a scaffold for synthesis of the second sequence. Cleavage of the linker under conditions suitable for hybridization of the separate siNA sequence strands results in formation of the double-stranded siNA molecule.

In another embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing one oligonucleotide sequence strand of the siNA molecule, wherein the sequence comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of another oligonucleotide sequence; (b) synthesizing a second oligonucleotide sequence having complementarity to the first sequence strand on the scaffold of (a), wherein the second sequence comprises the other strand of the double-stranded siNA molecule and wherein the second sequence further comprises a chemical moiety than can be used to isolate the attached oligonucleotide

sequence; (c) purifying the product of (b) utilizing the chemical moiety of the second oligonucleotide sequence strand under conditions suitable for isolating the full-length sequence comprising both siNA oligonucleotide strands connected by the cleavable linker and under conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions. In another embodiment, cleavage of the linker molecule in (c) above takes place after deprotection of the oligonucleotide. In another embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity or differing reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place either concomitantly or sequentially. In one embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group.

In another embodiment, the invention features a method for making a double-stranded siNA molecule in a single synthetic process comprising: (a) synthesizing an oligonucleotide having a first and a second sequence, wherein the first sequence is complementary to the second sequence, and the first oligonucleotide sequence is linked to the second sequence via a cleavable linker, and wherein a terminal 5'-protecting group, for example, a 5'-O-dimethoxytrityl group (5'-O-DMT) remains on the oligonucleotide having the second sequence; (b) deprotecting the oligonucleotide whereby the deprotection results in the cleavage of the linker joining the two oligonucleotide sequences; and (c) purifying the product of (b) under conditions suitable for isolating the double-stranded siNA molecule, for example using a trityl-on synthesis strategy as described herein.

In another embodiment, the method of synthesis of siNA molecules of the invention comprises the teachings of Scaringe *et al.*, US Patent Nos. 5,889,136; 6,008,400; and 6,111,086, incorporated by reference herein in their entirety.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications, for example, one or more chemical modifications having any of Formulae I-VII or any combination thereof that increases the nuclease resistance of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased nuclease resistance comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased nuclease resistance.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the sense and antisense strands of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the sense and antisense strands of the siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the sense and antisense strands of the siNA molecule.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target RNA sequence within a cell.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target DNA sequence within a cell.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulate the polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA construct.

In another embodiment, the invention features a method for generating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to a chemically-modified siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA molecule.

In one embodiment, the invention features chemically-modified siNA constructs that mediate RNAi against SARS in a cell, wherein the chemical modifications do not

significantly effect the interaction of siNA with a target RNA molecule, DNA molecule and/or proteins or other factors that are essential for RNAi in a manner that would decrease the efficacy of RNAi mediated by such siNA constructs.

In another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target RNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target RNA.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target DNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target DNA.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the cellular uptake of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules against SARS with improved cellular uptake comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved cellular uptake.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that increases the bioavailability of the siNA construct,

for example, by attaching polymeric conjugates such as polyethyleneglycol or equivalent conjugates that improve the pharmacokinetics of the siNA construct, or by attaching conjugates that target specific tissue types or cell types *in vivo*. Non-limiting examples of such conjugates are described in Vargeese *et al.*, U.S. Serial No. 10/201,394 incorporated by reference herein.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability, comprising (a) introducing a conjugate into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such conjugates can include ligands for cellular receptors, such as peptides derived from naturally occurring protein ligands; protein localization sequences, including cellular ZIP code sequences; antibodies; nucleic acid aptamers; vitamins and other co-factors, such as folate and N-acetylgalactosamine; polymers, such as polyethyleneglycol (PEG); phospholipids; cholesterol; polyamines, such as spermine or spermidine; and others.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically modified in a manner that it can no longer act as a guide sequence for efficiently mediating RNA interference and/or be recognized by cellular proteins that facilitate RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein the second sequence is designed or modified in a manner that prevents its entry into the RNAi pathway as a guide sequence or as a sequence that is complementary to a target nucleic acid (e.g., RNA) sequence. Such design or modifications are expected to enhance the activity of siNA and/or improve the specificity of siNA molecules of the invention. These modifications are also expected to minimize any off-target effects and/or associated toxicity.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is incapable of acting as a guide sequence for mediating RNA interference.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence does not have a terminal 5'-hydroxyl (5'-OH) or 5'-phosphate group.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end of said second sequence. In one embodiment, the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end and 3'-end of said second sequence. In one embodiment, each terminal cap moiety individually comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting

the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising (a) introducing one or more chemical modifications into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved specificity. In another embodiment, the chemical modification used to improve specificity comprises terminal cap modifications at the 5'-end, 3'-end, or both 5' and 3'-ends of the siNA molecule. The terminal cap modifications can comprise, for example, structures shown in **Figure 10** (e.g. inverted deoxyabasic moieties) or any other chemical modification that renders a portion of the siNA molecule (e.g. the sense strand) incapable of mediating RNA interference against an off target nucleic acid sequence. In a non-limiting example, a siNA molecule is designed such that only the antisense sequence of the siNA molecule can serve as a guide sequence for RISC mediated degradation of a corresponding target RNA sequence. This can be accomplished by rendering the sense sequence of the siNA inactive by introducing chemical modifications to the sense strand that preclude recognition of the sense strand as a guide sequence by RNAi machinery. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand of the siNA, or any other group that serves to render the sense strand inactive as a guide sequence for mediating RNA interference. These modifications, for example, can result in a molecule where the 5'-end of the sense strand no longer has a free 5'-hydroxyl (5'-OH) or a free 5'-phosphate group (e.g., phosphate, diphosphate, triphosphate, cyclic phosphate etc.). Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising introducing one or more chemical modifications into the structure of a siNA molecule that prevent a strand or portion of the siNA molecule from acting as a template or guide sequence for RNAi acitivity. In one embodiment, the inactive strand or sense region of the siNA molecule is the sense strand or sense region of the siNA molecule, i.e. the strand or region of the siNA that does not have

complementarity to the target nucleic acid sequence. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand or region of the siNA that does not comprise a 5'-hydroxyl (5'-OH) or 5'-phosphate group, or any other group that serves to render the sense strand or sense region inactive as a guide sequence for mediating RNA interference. Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22"chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for screening siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of unmodified siNA molecules, (b) screening the siNA molecules of step (a) under conditions suitable for isolating siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence, and (c) introducing chemical modifications (e.g. chemical modifications as described herein or as otherwise known in the art) into the active siNA molecules of (b). In one embodiment, the method further comprises re-screening the chemically modified siNA molecules of step (c) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

In one embodiment, the invention features a method for screening chemically modified siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of chemically modified siNA molecules (e.g. siNA molecules as described herein or as otherwise known in the art), and (b) screening the siNA molecules of step (a) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

The term "ligand" refers to any compound or molecule, such as a drug, peptide, hormone, or neurotransmitter, that is capable of interacting with another compound, such as a receptor, either directly or indirectly. The receptor that interacts with a ligand can be present on the surface of a cell or can alternately be an intercullular receptor. Interaction

of the ligand with the receptor can result in a biochemical reaction, or can simply be a physical interaction or association.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing an excipient formulation to a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such excipients include polymers such as cyclodextrins, lipids, cationic lipids, polyamines, phospholipids, nanoparticles, receptors, ligands, and others.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing nucleotides having any of Formulae I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

In another embodiment, polyethylene glycol (PEG) can be covalently attached to siNA compounds of the present invention. The attached PEG can be any molecular weight, preferably from about 2,000 to about 50,000 daltons (Da).

The present invention can be used alone or as a component of a kit having at least one of the reagents necessary to carry out the *in vitro* or *in vivo* introduction of RNA to test samples and/or subjects. For example, preferred components of the kit include a siNA molecule of the invention and a vehicle that promotes introduction of the siNA into cells of interest as described herein (e.g., using lipids and other methods of transfection known in the art, see for example Beigelman *et al,* US 6,395,713). The kit can be used for target validation, such as in determining gene function and/or activity, or in drug optimization, and in drug discovery (see for example Usman et al., USSN 60/402,996). Such a kit can also include instructions to allow a user of the kit to practice the invention.

The term "short interfering nucleic acid", "siNA", "short interfering RNA", "siRNA", "short interfering nucleic acid molecule", "short interfering oligonucleotide molecule", or "chemically-modified short interfering nucleic acid molecule" as used herein refers to any nucleic acid molecule capable of inhibiting or down regulating gene

expression or viral replication, for example by mediating RNA interference "RNAi" or gene silencing in a sequence-specific manner; see for example Zamore *et al.*, 2000, Cell, 101, 25-33; Bass, 2001, *Nature*, 411, 428-429; Elbashir *et al.*, 2001, *Nature*, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237; Hutvagner and Zamore, 2002, *Science*, 297, 2056-60; McManus *et al.*, 2002, *RNA*, 8, 842-850; Reinhart *et al.*, 2002, *Gene & Dev.*, 16, 1616-1626; and Reinhart & Bartel, 2002, *Science*, 297, 1831). Non limiting examples of siNA molecules of the invention are shown in **Figures 4-6,** and **Tables II and III** herein. For example the siNA can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for example wherein the double stranded region is about 19 base pairs); the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the siNA is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having

self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such siNA molecule does not require the presence within the siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.*, 2002, *Cell.*, 110, 563-574 and Schwarz *et al.*, 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate. In certain embodiments, the siNA molecule of the invention comprises separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic intercations, and/or stacking interactions. In certain embodiments, the siNA molecules of the invention comprise nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the siNA molecule of the invention interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene. As used herein, siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides and non-nucleotides. In certain embodiments, the short interfering nucleic acid molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. Applicant describes in certain embodiments short interfering nucleic acids that do not require the presence of

nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. The modified short interfering nucleic acid molecules of the invention can also be referred to as short interfering modified oligonucleotides "siMON." As used herein, the term siNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically-modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the invention can result from siNA mediated modification of chromatin structure to alter gene expression (see, for example, Verdel *et al.*, 2004, *Science*, 303, 672-676; Pal-Bhadra *et al.*, 2004, *Science*, 303, 669-672; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237).

In one embodiment, a siNA molecule of the invention is a duplex forming oligonucleotide "DFO", (see for example **Figures 14-15** and Vaish *et al.*, USSN 10/727,780 filed December 3, 2003).

In one embodiment, a siNA molecule of the invention is a multifunctional siNA, (see for example **Figures 16-22** and Jadhav *et al.*, USSN 60/543,480, filed February 10,

2004). The multifunctional siNA of the invention can comprise sequence targeting, for example, two regions of SARS RNA (see for example target sequences in **Tables II and III**) or alternately, SARS RNA and cellular RNA involved in SARS virus infection or replication. In another embodiment, a multifunctional siNA of the invention can comprise sequence targeting for example both viral genes encoding RNAi inhibitory factors and viral genes encoding viral structural proteins.

By "asymmetric hairpin" as used herein is meant a linear siNA molecule comprising an antisense region, a loop portion that can comprise nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g., about 19, 20, 21, or 22) nucleotides) and a loop region comprising about 4 to about 8 (e.g., about 4, 5, 6, 7, or 8) nucleotides, and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region. The asymmetric hairpin siNA molecule can also comprise a 5'-terminal phosphate group that can be chemically modified. The loop portion of the asymmetric hairpin siNA molecule can comprise nucleotides, non-nucleotides, linker molecules, or conjugate molecules as described herein.

By "asymmetric duplex" as used herein is meant a siNA molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex. For example, an asymmetric duplex siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g. about 19, 20, 21, or 22) nucleotides) and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region.

By "modulate" is meant that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or

activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the absence of the modulator. For example, the term "modulate" can mean "inhibit," but the use of the word "modulate" is not limited to this definition.

By “inhibit”, "down-regulate", or “reduce”, it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced below that observed in the absence of the nucleic acid molecules (e.g., siNA) of the invention. In one embodiment, inhibition, down-regulation or reduction with an siNA molecule is below that level observed in the presence of an inactive or attenuated molecule. In another embodiment, inhibition, down-regulation, or reduction with siNA molecules is below that level observed in the presence of, for example, an siNA molecule with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of gene expression with a nucleic acid molecule of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

By "gene", or "target gene", is meant, a nucleic acid that encodes an RNA, for example, nucleic acid sequences including, but not limited to, structural genes encoding a polypeptide. A gene or target gene can also encode a functional RNA (fRNA) or non-coding RNA (ncRNA), such as small temporal RNA (stRNA), micro RNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for siNA mediated RNA interference in modulating the activity of fRNA or ncRNA involved in functional or regulatory cellular processes. Abberant fRNA or ncRNA activity leading to disease can therefore be modulated by siNA molecules of the invention. siNA molecules targeting fRNA and ncRNA can also be used to manipulate or alter the genotype or phenotype of an organism or cell, by intervening in cellular processes such as genetic imprinting, transcription, translation, or nucleic acid processing (e.g., transamination, methylation etc.). The target gene can be a gene derived from a cell, an endogenous gene, a transgene, or exogenous genes such as genes of a pathogen, for example a virus,

which is present in the cell after infection thereof. The cell containing the target gene can be derived from or contained in any organism, for example a plant, animal, protozoan, virus, bacterium, or fungus. Non-limiting examples of plants include monocots, dicots, or gymnosperms. Non-limiting examples of animals include vertebrates or invertebrates. Non-limiting examples of fungi include molds or yeasts.

By "SARS" or "SARS virus" as used herein is meant the SARS virus or any protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome. The term "SARS" also includes nucleic acid molecules encoding RNA or protein(s) associated with the development and/or maintenance of SARS virus infection, such as nucleic acid molecules which encode SARS RNA or polypeptides (such as polynucleotides having Genbank Accession numbers shown in Table I), including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as genes involved in SARS pathways of gene expression and/or SARS activity. Also, the term "SARS" is meant to encompass SARS viral gene products and genes that modulate cellular targets for SARS virus infection, such as those described herein.

By "SARS protein" or "SARS virus protein" is meant, protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome or alternately, cellular proteins involved in SARS virus infection and/or replication.

By "homologous sequence" is meant, a nucleotide sequence that is shared by one or more polynucleotide sequences, such as genes, gene transcripts and/or non-coding polynucleotides. For example, a homologous sequence can be a nucleotide sequence that is shared by two or more genes encoding related but different proteins, such as different members of a gene family, different protein epitopes, different protein isoforms or completely divergent genes, such as a cytokine and its corresponding receptors. A homologous sequence can be a nucleotide sequence that is shared by two or more non-coding polynucleotides, such as noncoding DNA or RNA, regulatory sequences, introns, and sites of transcriptional control or regulation. Homologous sequences can also include conserved sequence regions shared by more than one polynucleotide sequence. Homology does not need to be perfect homology (e.g., 100%), as partially homologous sequences are also contemplated by the instant invention (e.g., 99%, 98%, 97%, 96%,

95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80% etc.).

By "conserved sequence region" is meant, a nucleotide sequence of one or more regions in a polynucleotide does not vary significantly between generations or from one biological system or organism to another biological system or organism. The polynucleotide can include both coding and non-coding DNA and RNA.

By "sense region" is meant a nucleotide sequence of a siNA molecule having complementarity to an antisense region of the siNA molecule. In addition, the sense region of a siNA molecule can comprise a nucleic acid sequence having homology with a target nucleic acid sequence.

By "antisense region" is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can optionally comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule.

By "target nucleic acid" is meant any nucleic acid sequence whose expression or activity is to be modulated. The target nucleic acid can be DNA or RNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.*, 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.*, 1986, *Proc. Nat. Acad. Sci.* USA 83:9373-9377; Turner *et al.*, 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, or 10 nucleotides out of a total of 10 nucleotides in the first oligonuelcotide being based paired to a second nucleic acid sequence having 10 nucleotides represents 50%, 60%, 70%, 80%, 90%, and

100% complementary respectively). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

The siNA molecules of the invention represent a novel therapeutic approach to treat various diseases and conditions, including SARS virus infection, acute respiratory failure, viral pneumonia, and any other indications that can respond to the level of SARS in a cell or tissue. The reduction of SARS expression and thus reduction in the level of the respective protein relieves, to some extent, the symptoms of the disease or condition.

In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently about 18 to about 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (*e.g.*, about 17, 18, 19, 20, 21, 22 or 23). In yet another embodiment, siNA molecules of the invention comprising hairpin or circular structures are about 35 to about 55 (*e.g.*, about 35, 40, 45, 50 or 55) nucleotides in length, or about 38 to about 44 (*e.g.*, 38, 39, 40, 41, 42, 43 or 44) nucleotides in length and comprising about 16 to about 22 (*e.g.*, about 16, 17, 18, 19, 20, 21 or 22) base pairs. Exemplary siNA molecules of the invention are shown in **Table II**. Exemplary synthetic siNA molecules of the invention are shown in **Table III** and/or **Figures 4-5**.

As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, e.g., specifically does not refer to a human. The cell can be present in an organism, e.g., birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell can be prokaryotic (e.g., bacterial cell) or eukaryotic (e.g., mammalian or plant cell). The cell can be of somatic or germ line origin, totipotent or pluripotent, dividing or non-dividing. The cell can also be derived from or can comprise a gamete or embryo, a stem cell, or a fully differentiated cell.

The siNA molecules of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, infusion pump or stent, with or

without their incorporation in biopolymers. In particular embodiments, the nucleic acid molecules of the invention comprise sequences shown in **Tables II-III** and/or **Figures 4-5**. Examples of such nucleic acid molecules consist essentially of sequences defined in these tables and figures. Furthermore, the chemically modified constructs described in **Table IV** can be applied to any siNA sequence of the invention.

In another aspect, the invention provides mammalian cells containing one or more siNA molecules of this invention. The one or more siNA molecules can independently be targeted to the same or different sites.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position of a β-D-ribo-furanose moiety. The terms include double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siNA or internally, for example at one or more nucleotides of the RNA. Nucleotides in the RNA molecules of the instant invention can also comprise non-standard nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as analogs or analogs of naturally-occurring RNA.

By "subject" is meant an organism, which is a donor or recipient of explanted cells or the cells themselves. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells.

The term "phosphorothioate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise a sulfur atom. Hence, the term phosphorothioate refers to both phosphorothioate and phosphorodithioate internucleotide linkages.

The term "phosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise an acetyl or protected acetyl group.

The term "thiophosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z comprises an acetyl or protected acetyl group and W comprises a sulfur atom or alternately W comprises an acetyl or protected acetyl group and Z comprises a sulfur atom.

The term "universal base" as used herein refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research,* 29, 2437-2447).

The term "acyclic nucleotide" as used herein refers to any nucleotide having an acyclic ribose sugar, for example where any of the ribose carbons (C1, C2, C3, C4, or C5), are independently or in combination absent from the nucleotide.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed herein (e.g., cancers and othe proliferative conditions). For example, to treat a particular disease or condition, the siNA molecules can be administered to a subject or can be administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the siNA molecules can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic agents to treat a disease or condition. Non-limiting examples of other therapeutic agents that can be readily combined with a siNA molecule of the invention are enzymatic nucleic acid molecules, allosteric nucleic acid molecules, antisense, decoy, or aptamer nucleic acid molecules, antibodies such as monoclonal antibodies, small molecules, and other organic and/or inorganic compounds including metals, salts and ions.

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention, in a manner which allows expression of the siNA molecule. For example, the vector can contain sequence(s) encoding both strands of a siNA molecule comprising a duplex. The vector can also contain sequence(s) encoding a single nucleic acid molecule that is self-complementary and thus forms a siNA molecule. Non-limiting examples of such expression vectors are described in Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725.

In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

In yet another embodiment, the expression vector of the invention comprises a sequence for a siNA molecule having complementarity to a RNA molecule referred to by a Genbank Accession numbers, for example Genbank Accession Nos. shown in **Table I**.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more siNA molecules, which can be the same or different.

In another aspect of the invention, siNA molecules that interact with target RNA molecules and down-regulate gene encoding target RNA molecules (for example target RNA molecules referred to by Genbank Accession numbers herein) are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecules bind and down-regulate gene function or expression via RNA interference (RNAi). Delivery of siNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into

the subject, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a non-limiting example of a scheme for the synthesis of siNA molecules. The complementary siNA sequence strands, strand 1 and strand 2, are synthesized in tandem and are connected by a cleavable linkage, such as a nucleotide succinate or abasic succinate, which can be the same or different from the cleavable linker used for solid phase synthesis on a solid support. The synthesis can be either solid phase or solution phase, in the example shown, the synthesis is a solid phase synthesis. The synthesis is performed such that a protecting group, such as a dimethoxytrityl group, remains intact on the terminal nucleotide of the tandem oligonucleotide. Upon cleavage and deprotection of the oligonucleotide, the two siNA strands spontaneously hybridize to form a siNA duplex, which allows the purification of the duplex by utilizing the properties of the terminal protecting group, for example by applying a trityl on purification method wherein only duplexes/oligonucleotides with the terminal protecting group are isolated.

Figure 2 shows a MALDI-TOF mass spectrum of a purified siNA duplex synthesized by a method of the invention. The two peaks shown correspond to the predicted mass of the separate siNA sequence strands. This result demonstrates that the siNA duplex generated from tandem synthesis can be purified as a single entity using a simple trityl-on purification methodology.

Figure 3 shows a non-limiting proposed mechanistic representation of target RNA degradation involved in RNAi. Double-stranded RNA (dsRNA), which is generated by RNA-dependent RNA polymerase (RdRP) from foreign single-stranded RNA, for example viral, transposon, or other exogenous RNA, activates the DICER enzyme that in

turn generates siNA duplexes. Alternately, synthetic or expressed siNA can be introduced directly into a cell by appropriate means. An active siNA complex forms which recognizes a target RNA, resulting in degradation of the target RNA by the RISC endonuclease complex or in the synthesis of additional RNA by RNA-dependent RNA polymerase (RdRP), which can activate DICER and result in additional siNA molecules, thereby amplifying the RNAi response.

Figure 4A-F shows non-limiting examples of chemically-modified siNA constructs of the present invention. In the figure, N stands for any nucleotide (adenosine, guanosine, cytosine, uridine, or optionally thymidine, for example thymidine can be substituted in the overhanging regions designated by parenthesis (N N). Various modifications are shown for the sense and antisense strands of the siNA constructs.

Figure 4A: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4B: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all

pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the sense and antisense strand.

Figure 4C: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4D: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are

2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4E: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4F: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and having one 3'-terminal phosphorothioate internucleotide linkage and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-deoxy nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,

deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand. The antisense strand of constructs A-F comprise sequence complementary to any target nucleic acid sequence of the invention. Furthermore, when a glyceryl moiety (L) is present at the 3'-end of the antisense strand for any construct shown in Figure 4 A-F, the modified internucleotide linkage is optional.

Figure 5A-F shows non-limiting examples of specific chemically-modified siNA sequences of the invention. **A-F** applies the chemical modifications described in **Figure 4A-F** to a SARS virus siNA sequence. Such chemical modifications can be applied to any SARS sequence and/or SARS polymorphism sequence.

Figure 6 shows non-limiting examples of different siNA constructs of the invention. The examples shown (constructs 1, 2, and 3) have 19 representative base pairs; however, different embodiments of the invention include any number of base pairs described herein. Bracketed regions represent nucleotide overhangs, for example comprising about 1, 2, 3, or 4 nucleotides in length, preferably about 2 nucleotides. Constructs 1 and 2 can be used independently for RNAi activity. Construct 2 can comprise a polynucleotide or non-nucleotide linker, which can optionally be designed as a biodegradable linker. In one embodiment, the loop structure shown in construct 2 can comprise a biodegradable linker that results in the formation of construct 1 *in vivo* and/or *in vitro*. In another example, construct 3 can be used to generate construct 2 under the same principle wherein a linker is used to generate the active siNA construct 2 *in vivo* and/or *in vitro*, which can optionally utilize another biodegradable linker to generate the active siNA construct 1 *in vivo* and/or *in vitro*. As such, the stability and/or activity of the siNA constructs can be modulated based on the design of the siNA construct for use *in vivo* or *in vitro* and/or *in vitro*.

Figure 7A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate siNA hairpin constructs.

Figure 7A: A DNA oligomer is synthesized with a 5'-restriction site (R1) sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, which is followed by a loop sequence of defined sequence (X), comprising, for example, about 3 to about 10 nucleotides.

Figure 7B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence that will result in a siNA transcript having specificity for a SARS target sequence and having self-complementary sense and antisense regions.

Figure 7C: The construct is heated (for example to about 95°C) to linearize the sequence, thus allowing extension of a complementary second DNA strand using a primer to the 3'-restriction sequence of the first strand. The double-stranded DNA is then inserted into an appropriate vector for expression in cells. The construct can be designed such that a 3'-terminal nucleotide overhang results from the transcription, for example by engineering restriction sites and/or utilizing a poly-U termination region as described in Paul *et al.*, 2002, *Nature Biotechnology*, 29, 505-508.

Figure 8A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate double-stranded siNA constructs.

Figure 8A: A DNA oligomer is synthesized with a 5'-restriction (R1) site sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, and which is followed by a 3'-restriction site (R2) which is adjacent to a loop sequence of defined sequence (X).

Figure 8B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence.

Figure 8C: The construct is processed by restriction enzymes specific to R1 and R2 to generate a double-stranded DNA which is then inserted into an appropriate vector for expression in cells. The transcription cassette is designed such that a U6 promoter region flanks each side of the dsDNA which generates the separate sense and antisense

strands of the siNA. Poly T termination sequences can be added to the constructs to generate U overhangs in the resulting transcript.

Figure 9A-E is a diagrammatic representation of a method used to determine target sites for siNA mediated RNAi within a particular target nucleic acid sequence, such as messenger RNA.

Figure 9A: A pool of siNA oligonucleotides are synthesized wherein the antisense region of the siNA constructs has complementarity to target sites across the target nucleic acid sequence, and wherein the sense region comprises sequence complementary to the antisense region of the siNA.

Figure 9B&C: (Figure 9B) The sequences are pooled and are inserted into vectors such that **(Figure 9C)** transfection of a vector into cells results in the expression of the siNA.

Figure 9D: Cells are sorted based on phenotypic change that is associated with modulation of the target nucleic acid sequence.

Figure 9E: The siNA is isolated from the sorted cells and is sequenced to identify efficacious target sites within the target nucleic acid sequence.

Figure 10 shows non-limiting examples of different stabilization chemistries (1-10) that can be used, for example, to stabilize the 3'-end of siNA sequences of the invention, including **(1)** [3-3']-inverted deoxyribose; **(2)** deoxyribonucleotide; **(3)** [5'-3']-3'-deoxyribonucleotide; **(4)** [5'-3']-ribonucleotide; **(5)** [5'-3']-3'-O-methyl ribonucleotide; **(6)** 3'-glyceryl; **(7)** [3'-5']-3'-deoxyribonucleotide; **(8)** [3'-3']-deoxyribonucleotide; **(9)** [5'-2']-deoxyribonucleotide; and **(10)** [5-3']-dideoxyribonucleotide. In addition to modified and unmodified backbone chemistries indicated in the figure, these chemistries can be combined with different backbone modifications as described herein, for example, backbone modifications having Formula I. In addition, the 2'-deoxy nucleotide shown 5' to the terminal modifications shown can be another modified or unmodified nucleotide or non-nucleotide described herein, for example modifications having any of Formulae I-VII or any combination thereof.

Figure 11 shows a non-limiting example of a strategy used to identify chemically modified siNA constructs of the invention that are nuclease resistance while preserving the ability to mediate RNAi activity. Chemical modifications are introduced into the siNA construct based on educated design parameters (e.g. introducing 2'-mofications, base modifications, backbone modifications, terminal cap modifications etc). The modified construct in tested in an appropriate system (e.g. human serum for nuclease resistance, shown, or an animal model for PK/delivery parameters). In parallel, the siNA construct is tested for RNAi activity, for example in a cell culture system such as a luciferase reporter assay). Lead siNA constructs are then identified which possess a particular characteristic while maintaining RNAi activity, and can be further modified and assayed once again. This same approach can be used to identify siNA-conjugate molecules with improved pharmacokinetic profiles, delivery, and RNAi activity.

Figure 12 shows non-limiting examples of phosphorylated siNA molecules of the invention, including linear and duplex constructs and asymmetric derivatives thereof.

Figure 13 shows non-limiting examples of chemically modified terminal phosphate groups of the invention.

Figure 14A shows a non-limiting example of methodology used to design self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are identifed in a target nucleic acid sequence. (i) A palindrome or repeat sequence is identified in a nucleic acid target sequence. (ii) A sequence is designed that is complementary to the target nucleic acid sequence and the palindrome sequence. (iii) An inverse repeat sequence of the non-palindrome/repeat portion of the complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complmentary DFO molecule comprising sequence complementary to the nucleic acid target. (iv) The DFO molecule can self-assemble to form a double stranded oligonucleotide. **Figure 14B** shows a non-limiting representative example of a duplex forming oligonucleotide sequence. **Figure 14C** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence. **Figure 14D** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence followed by interaction with a target nucleic acid sequence resulting in modulation of gene expression.

Figure 15 shows a non-limiting example of the design of self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are incorporated into the DFO constructs that have sequence complementary to any target nucleic acid sequence of interest. Incorporation of these palindrome/repeat sequences allow the design of DFO constructs that form duplexes in which each strand is capable of mediating modulation of target gene expression, for example by RNAi. First, the target sequence is identified. A complementary sequence is then generated in which nucleotide or non-nucleotide modifications (shown as X or Y) are introduced into the complementary sequence that generate an artificial palindrome (shown as XYXYXY in the Figure). An inverse repeat of the non-palindrome/repeat complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complmentary DFO comprising sequence complementary to the nucleic acid target. The DFO can self-assemble to form a double stranded oligonucleotide.

Figure 16 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 16A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 16B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 17 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 17A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 17B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 16**.

Figure 18 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifuctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 18A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA, and

wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 18B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 19 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifuctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 19A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 19B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a

second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 18**.

Figure 20 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid molecules, such as separate RNA molecules encoding differing proteins, for example, differing viral strains, a virus and a cellular protein involved in viral infection or replication, or differing proteins involved in a common or divergent biologic pathway that is implicated in the maintenance of progression of disease. Each strand of the multifunctional siNA construct comprises a region having complementarity to separate target nucleic acid molecules. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interferance mediated cleavage of its corresponding target. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 21 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid seqeunces within the same target nucleic acid molecule, such as alternate coding regions of a RNA, coding and non-coding regions of a RNA, or alternate splice variant regions of a RNA. Each strand of the multifunctional siNA construct comprises a region having complementarity to the separate regions of the target nucleic acid molecule. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interferance mediated cleavage of its corresponding target region. These

design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

DETAILED DESCRIPTION OF THE INVENTION

Mechanism of Action of Nucleic Acid Molecules of the Invention

The discussion that follows discusses the proposed mechanism of RNA interference mediated by short interfering RNA as is presently known, and is not meant to be limiting and is not an admission of prior art. Applicant demonstrates herein that chemically-modified short interfering nucleic acids possess similar or improved capacity to mediate RNAi as do siRNA molecules and are expected to possess improved stability and activity *in vivo*; therefore, this discussion is not meant to be limiting only to siRNA and can be applied to siNA as a whole. By "improved capacity to mediate RNAi" or “improved RNAi activity” is meant to include RNAi activity measured *in vitro* and/or *in vivo* where the RNAi activity is a reflection of both the ability of the siNA to mediate RNAi and the stability of the siNAs of the invention. In this invention, the product of these activities can be increased *in vitro* and/or *in vivo* compared to an all RNA siRNA or a siNA containing a plurality of ribonucleotides. In some cases, the activity or stability of the siNA molecule can be decreased (i.e., less than ten-fold), but the overall activity of the siNA molecule is enhanced *in vitro* and/or *in vivo*.

RNA interference refers to the process of sequence specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Fire *et al.*, 1998, *Nature*, 391, 806). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla (Fire *et al.*, 1999,

Trends Genet., 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2', 5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as Dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Berstein *et al.*, 2001, *Nature,* 409, 363). Short interfering RNAs derived from Dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes. Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science,* 293, 834). The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence homologous to the siRNA. Cleavage of the target RNA takes place in the middle of the region complementary to the guide sequence of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). In addition, RNA interference can also involve small RNA (e.g., micro-RNA or miRNA) mediated gene silencing, presumably though cellular mechanisms that regulate chromatin structure and thereby prevent transcription of target gene sequences (see for example Allshire, 2002, *Science,* 297, 1818-1819; Volpe *et al.*, 2002, *Science,* 297, 1833-1837; Jenuwein, 2002, *Science,* 297, 2215-2218; and Hall *et al.*, 2002, *Science,* 297, 2232-2237). As such, siNA molecules of the invention can be used to mediate gene silencing via interaction with RNA transcripts or alternately by interaction with particular gene sequences, wherein such interaction results in gene silencing either at the transcriptional level or post-transcriptional level.

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature,* 391, 806, were the first to observe RNAi in *C. elegans*. Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.*, 2000, *Nature,* 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature,* 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in Drosophila embryonic lysates has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21 nucleotide siRNA duplexes are most active when containing two 2-nucleotide 3'-terminal nucleotide overhangs. Furthermore, substitution of one or both siRNA strands with 2'-deoxy or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of 3'-terminal siRNA nucleotides with deoxy nucleotides was shown to be tolerated. Mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell,* 107, 309); however, siRNA molecules lacking a 5'-phosphate are active when introduced exogenously, suggesting that 5'-phosphorylation of siRNA constructs may occur *in vivo*.

Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, individual siNA oligonucleotide sequences or siNA sequences synthesized in tandem) are preferably used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid

to invade targeted regions of protein and/or RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

Oligonucleotides (*e.g.*, certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol Bioeng.*, 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 second coupling step for 2'-deoxy nucleotides or 2'-deoxy-2'-fluoro nucleotides. **Table V** outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μL of 0.11 M = 4.4 μmol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μL of 0.25 M = 10 μmol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained

from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA-based oligonucleotides is performed as follows: the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aqueous methylamine (1 mL) at 65 °C for 10 minutes. After cooling to –20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA including certain siNA molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. **Table V** outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 μL of 0.11 M = 13.2 μmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 μL of 0.25 M = 30 μmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems,

Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide0.05 M in acetonitrile) is used.

Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to –20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 µL of a solution of 1.5 mL N-methylpyrrolidinone, 750 µL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C. After 1.5 h, the oligomer is quenched with 1.5 M NH_4HCO_3.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 minutes. The vial is brought to room temperature TEA•3HF (0.1 mL) is added and the vial is heated at 65 °C for 15 minutes. The sample is cooled at –20 °C and then quenched with 1.5 M NH_4HCO_3.

For purification of the trityl-on oligomers, the quenched NH_4HCO_3 solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is detritylated with 0.5% TFA for 13 minutes. The cartridge is then washed again with

water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96-well format.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No. WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204), or by hybridization following synthesis and/or deprotection.

The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are synthesized as a single contiguous oligonucleotide fragment or strand-separated by a cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker. The tandem synthesis of siNA as described herein can be readily adapted to both multiwell/multiplate synthesis platforms such as 96 well or similarly larger multi-well platforms. The tandem synthesis of siNA as described herein can also be readily adapted to large scale synthesis platforms employing batch reactors, synthesis columns and the like.

A siNA molecule can also be assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment includes the antisense region of the RNA molecule.

The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-fluoro, 2'-*O*-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). siNA constructs can

be purified by gel electrophoresis using general methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott *et al., supra*, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

In another aspect of the invention, siNA molecules of the invention are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) can prevent their degradation by serum ribonucleases, which can increase their potency (see *e.g.*, Eckstein *et al.*, International Publication No. WO 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken *et al.*, 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; Gold *et al.*, U.S. Pat. No. 6,300,074; and Burgin *et al., supra;* all of which are incorporated by reference herein). All of the above references describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules described herein. Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired.

There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-fluoro, 2'-*O*-methyl, 2'-O-allyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992,

TIBS. 17, 34; Usman *et al.,* 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al., International Publication* PCT No. WO 92/07065; Perrault *et al. Nature*, 1990, *344*, 565-568; Pieken *et al. Science*, 1991, *253*, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, *17*, 334-339; Usman *et al. International Publication* PCT No. WO 93/15187; Sproat, *U.S. Pat.* No. 5,334,711 and Beigelman *et al.,* 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, International PCT publication No. WO 97/26270; Beigelman *et al.*, U.S. Pat. No. 5,716,824; Usman *et al.,* U.S. Pat. No. 5,627,053; Woolf *et al.*, International PCT Publication No. WO 98/13526; Thompson *et al.,* USSN 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi is cells is not significantly inhibited.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications can cause some toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity, resulting in increased efficacy and higher specificity of these molecules.

Short interfering nucleic acid (siNA) molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more resistant to nucleases than an unmodified nucleic acid. Accordingly, the *in vitro* and/or *in vivo* activity should not be significantly lowered. In cases in which modulation is the

goal, therapeutic nucleic acid molecules delivered exogenously should optimally be stable within cells until translation of the target RNA has been modulated long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19 (incorporated by reference herein)) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability, as described above.

In one embodiment, nucleic acid molecules of the invention include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands. In another embodiment, nucleic acid molecules of the invention include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of siNA molecules of the invention. Such conjugates and/or complexes can be used to facilitate delivery of siNA molecules into a biological system, such as a cell. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel conjugates and complexes for the delivery of molecules, including, but not limited to, small molecules, lipids, cholesterol, phospholipids, nucleosides, nucleotides, nucleic

acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers. These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker molecules.

The term "biodegradable linker" as used herein, refers to a nucleic acid or non-nucleic acid linker molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule to a siNA molecule of the invention or the sense and antisense strands of a siNA molecule of the invention. The biodegradable linker is designed such that its stability can be modulated for a particular purpose, such as delivery to a particular tissue or cell type. The stability of a nucleic acid-based biodegradable linker molecule can be modulated by using various chemistries, for example combinations of ribonucleotides, deoxyribonucleotides, and chemically-modified nucleotides, such as 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino, 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus-based linkage, for example, a phosphoramidate or phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein, refers to compounds or molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active siNA molecules either alone or in

combination with other molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, cholesterol, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus-containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

Therapeutic nucleic acid molecules (*e.g.*, siNA molecules) delivered exogenously optimally are stable within cells until reverse transcription of the RNA has been modulated long enough to reduce the levels of the RNA transcript. The nucleic acid molecules are resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In yet another embodiment, siNA molecules having chemical modifications that maintain or enhance enzymatic activity of proteins involved in RNAi are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acids. Thus, *in vitro* and/or *in vivo* the activity should not be significantly lowered.

Use of the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (*e.g.*, multiple siNA molecules targeted to different genes; nucleic acid molecules coupled with known small molecule modulators; or intermittent treatment with combinations of molecules, including different motifs and/or other chemical or

biological molecules). The treatment of subjects with siNA molecules can also include combinations of different types of nucleic acid molecules, such as enzymatic nucleic acid molecules (ribozymes), allozymes, antisense, 2,5-A oligoadenylate, decoys, and aptamers.

In another aspect a siNA molecule of the invention comprises one or more 5' and/or a 3'- cap structure, for example on only the sense siNA strand, the antisense siNA strand, or both siNA strands.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see, for example, Adamic *et al.*, U.S. Pat. No. 5,998,203, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide; carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety.

Non-limiting examples of the 3'-cap include, but are not limited to, glyceryl, inverted deoxy abasic residue (moiety), 4', 5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate; 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide

moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine and therefore lacks a base at the 1'-position.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino, or SH. The term also includes alkenyl groups that are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. More preferably, it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, $N(CH_3)_2$, amino, or SH. The term "alkyl" also includes alkynyl groups that have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably, it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino or SH.

Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group that has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see, for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra*, all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090;

Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents.

In one embodiment, the invention features modified siNA molecules, with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications, see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties,* in *Modern Synthetic Methods,* VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides,* in *Carbohydrate Modifications in Antisense Research,* ACS, 24-39.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, see for example Adamic *et al.*, U.S. Pat. No. 5,998,203.

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, or uracil joined to the 1' carbon of β-D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. Non-limiting examples of modified nucleotides are shown by Formulae I-VII and/or other modifications described herein.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH_2 or 2'-*O*- NH_2, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.*, U.S. Pat. No. 5,672,695 and Matulic-Adamic *et al.*, U.S. Pat. No. 6,248,878, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid siNA structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro*, stability, and ease of introduction of such oligonucleotides to the target site, *e.g.*, to

enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Administration of Nucleic Acid Molecules

A siRNA molecule of the invention can be adapted for use to treat for example SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue, alone or in combination with other therapies. For example, a siNA molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, *Trends Cell Bio.*, 2, 139; *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995, Maurer *et al.*, 1999, *Mol. Membr. Biol.*, 16, 129-140; Hofland and Huang, 1999, *Handb. Exp. Pharmacol.*, 137, 165-192; and Lee *et al.*, 2000, *ACS Symp. Ser.*, 752, 184-192, all of which are incorporated herein by reference. Beigelman *et al.*, U.S. Pat. No. 6,395,713 and Sullivan *et al.*, PCT WO 94/02595 further describe the general methods for delivery of nucleic acid molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins (see for example Gonzalez *et al.*, 1999, *Bioconjugate Chem.*, 10, 1068-1074; Wang *et al.*, International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLCA microspheres (see for example US Patent 6,447,796 and US Patent Application Publication No. US 2002130430), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.

Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump.

In one embodiment, the nucleic acid molecules or the invention are administered via pulmonary delivery, such as by inhalation of an aerosol or spray dried formulation administered by an inhalation device or nebulizer, providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues. Solid particulate compositions containing respirable dry particles of micronized nucleic acid compositions can be prepared by grinding dried or lyophilized nucleic acid compositions, and then passing the micronized composition through, for example, a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising the nucleic acid compositions of the invention can optionally contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which can be blended with the nucleic acid compound in any suitable ratio, such as a 1 to 1 ratio by weight.

Aerosols of liquid particles comprising a nucleic acid composition of the invention can be produced by any suitable means, such as with a nebulizer (see for example US 4,501,729). Nebulizers are commercially available devices which transform solutions or suspensions of an active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride or other suitable salts. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, anti-oxidants, flavorings, volatile oils, buffering agents and emulsifiers and other formulation surfactants. The aerosols of solid particles comprising the active composition and surfactant can likewise be produced with any solid particulate aerosol generator. Aerosol generators for administering solid particulate therapeutics to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a therapeutic composition at a rate

suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which can be delivered by means of an insufflator. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, emulsifiers and other formulation surfactants, such as oleic acid or sorbitan trioleate, anti-oxidants and suitable flavoring agents. Other methods for pulmonary delivery are described in, for example US Patent Application No. 20040037780, and US Patent Nos. 6,592,904; 6,582,728; 6,565,885.

In one embodiment, a siNA molecule of the invention is complexed with membrane disruptive agents such as those described in U.S. Patent Appliaction Publication No. 20010007666, incorporated by reference herein in its entirety including the drawings. In another embodiment, the membrane disruptive agent or agents and the siNA molecule are also complexed with a cationic lipid or helper lipid molecule, such as those lipids described in U.S. Patent No. 6,235,310, incorporated by reference herein in its entirety including the drawings.

Thus, the invention features a pharmaceutical composition comprising one or more nucleic acid(s) of the invention in an acceptable carrier, such as a stabilizer, buffer, and

the like. The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable administration, and the other compositions known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell to which the negatively charged nucleic acid is desirable for delivery). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the siNA molecules of the invention to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation that can facilitate the

association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cells producing excess repeat expansion genes.

By "pharmaceutically acceptable formulation" is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85),; biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery (Emerich, DF *et al*, 1999, *Cell Transplant*, 8, 47-58); and loaded nanoparticles, such as those made of polybutylcyanoacrylate. Other non-limiting examples of delivery strategies for the nucleic acid molecules of the instant invention include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596; Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058.

The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al. Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al., Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al., Science* 1995, 267, 1275-1276; Oku *et al.*,1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al., J. Biol. Chem.* 1995, 42, 24864-24870; Choi *et al.*, International PCT

Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985), hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors that those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically

acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain

aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a

demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per subject per day). The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration,

and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

In one embodiment, the invention comprises compositions suitable for administering nucleic acid molecules of the invention to specific cell types. For example, the asialoglycoprotein receptor (ASGPr) (Wu and Wu, 1987, *J. Biol. Chem.* 262, 4429-4432) is unique to hepatocytes and binds branched galactose-terminal glycoproteins, such as asialoorosomucoid (ASOR). In another example, the folate receptor is overexpressed in many cancer cells. Binding of such glycoproteins, synthetic glycoconjugates, or folates to the receptor takes place with an affinity that strongly depends on the degree of branching of the oligosaccharide chain, for example, triatennary structures are bound with greater affinity than biatenarry or monoatennary chains (Baenziger and Fiete, 1980, *Cell,* 22, 611-620; Connolly *et al.*, 1982, *J. Biol. Chem.*, 257, 939-945). Lee and Lee, 1987, *Glycoconjugate J.*, 4, 317-328, obtained this high specificity through the use of N-acetyl-D-galactosamine as the carbohydrate moiety, which has higher affinity for the receptor, compared to galactose. This "clustering effect" has also been described for the binding and uptake of mannosyl-terminating glycoproteins or glycoconjugates (Ponpipom *et al.*, 1981, *J. Med. Chem.*, 24, 1388-1395). The use of galactose, galactosamine, or folate based conjugates to transport exogenous compounds across cell membranes can provide a targeted delivery approach to, for example, the treatment of liver disease, cancers of the liver, or other cancers. The use of bioconjugates can also provide a reduction in the required dose of therapeutic compounds required for treatment. Furthermore, therapeutic bioavialability,

pharmacodynamics, and pharmacokinetic parameters can be modulated through the use of nucleic acid bioconjugates of the invention. Non-limiting examples of such bioconjugates are described in Vargeese *et al.*, USSN 10/201,394, filed August 13, 2001; and Matulic-Adamic *et al.*, USSN 10/151,116, filed May 17, 2002. In one embodiment, nucleic acid molecules of the invention are complexed with or covalently attached to nanoparticles, such as Hepatitis B virus S, M, or L evelope proteins (see for example Yamado *et al.*, 2003, *Nature Biotechnology*, 21, 885). In one embodiment, nucleic acid molecules of the invention are delivered with specificity for human tumor cells, specifically non-apoptotic human tumor cells including for example T-cells, hepatocytes, breast carcinoma cells, ovarian carcinoma cells, melanoma cells, intestinal epithelial cells, prostate cells, testicular cells, non-small cell lung cancers, small cell lung cancers, etc.

Alternatively, certain siNA molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.*, Izant and Weintraub, 1985, *Science*, 229, 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci.*, USA 83, 399; Scanlon *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992, *J. Virol.*, 66, 1432-41; Weerasinghe *et al.*, 1991, *J. Virol.*, 65, 5531-4; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science*, 247, 1222-1225; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856.

In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited

to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. In another embodiment, pol III based constructs are used to express nucleic acid molecules of the invention (see for example Thompson, U.S. Pats. Nos. 5,902,880 and 6,146,886). The recombinant vectors capable of expressing the siNA molecules can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.,* 1996, *TIG.,* 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the instant invention. The expression vector can encode one or both strands of a siNA duplex, or a single self-complementary strand that self hybridizes into a siNA duplex. The nucleic acid sequences encoding the siNA molecules of the instant invention can be operably linked in a manner that allows expression of the siNA molecule (see for example Paul *et al.,* 2002, *Nature Biotechnology,* 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology,* 19, 497; Lee *et al.,* 2002, *Nature Biotechnology,* 19, 500; and Novina *et al.,* 2002, *Nature Medicine,* advance online publication doi:10.1038/nm725).

In another aspect, the invention features an expression vector comprising: a) a transcription initiation region (*e.g.,* eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.,* eukaryotic pol I, II or III termination region); and c) a nucleic acid sequence encoding at least one of the siNA molecules of the instant invention,wherein said sequence is operably linked to said initiation region and said termination region in a manner that allows expression and/or delivery of the siNA molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the siNA of the invention; and/or an intron (intervening sequences).

Transcription of the siNA molecule sequences can be driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO J.*, 11, 4411-8; Lisziewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as siNA in cells (Thompson *et al., supra*; Couture and Stinchcomb, *1996, supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above siNA transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, *1996, supra)*.

In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the siNA molecules of the invention in a manner that allows expression of that siNA molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; and c) a nucleic acid sequence encoding at least one strand of the siNA molecule,

wherein the sequence is operably linked to the initiation region and the termination region in a manner that allows expression and/or delivery of the siNA molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; and d) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the open reading frame and the termination region in a manner that allows expression and/or delivery of the siNA molecule. In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; and d) a nucleic acid sequence encoding at least one siNA molecule, wherein the sequence is operably linked to the initiation region, the intron and the termination region in a manner which allows expression and/or delivery of the nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; and e) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the intron, the open reading frame and the termination region in a manner which allows expression and/or delivery of the siNA molecule.

SARS virus biology and biochemistry

The following discussion is adapted from the report, "Preliminary Clinical Description of Severe Acute Respiratory Syndrome", World Health Organization, Geneva, Switzerland, available at the Centers for Disease Control and Prevention website.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV). SARS was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the SARS

global outbreak of 2003 was contained. According to the World Health Organization (WHO), a total of 8,098 people worldwide became sick with SARS during the 2003 outbreak. Of these, 774 died.

The incubation period for SARS is typically 2--7 days; however, isolated reports have suggested an incubation period as long as 10 days. The illness begins generally with a prodrome of fever (>100.4°F [>38.0°C]). Fever often is high, sometimes is associated with chills and rigors, and might be accompanied by other symptoms, including headache, malaise, and myalgia. At the onset of illness, some persons have mild respiratory symptoms. Typically, rash and neurologic or gastrointestinal findings are absent; however, some patients have reported diarrhea during the febrile prodrome.

After 3--7 days, a lower respiratory phase begins with the onset of a dry, nonproductive cough or dyspnea, which might be accompanied by or progress to hypoxemia. In 10%--20% of cases, the respiratory illness is severe enough to require intubation and mechanical ventilation. Death may result from progressive respiratory failure due to alveolar damage. The case-fatality rate among persons with illness meeting the current WHO case definition of SARS is approximately 3%.

Chest radiographs might be normal during the febrile prodrome and throughout the course of illness. However, in a substantial proportion of patients, the respiratory phase is characterized by early focal interstitial infiltrates progressing to more generalized, patchy, interstitial infiltrates. Some chest radiographs from patients in the late stages of SARS also have shown areas of consolidation.

Early in the course of disease, the absolute lymphocyte count is often decreased. Overall white blood cell counts have generally been normal or decreased. At the peak of the respiratory illness, approximately 50% of patients have leukopenia and thrombocytopenia or low-normal platelet counts (50,000--150,000/μL). Early in the respiratory phase, elevated creatine phosphokinase levels (as high as 3,000 IU/L) and hepatic transaminases (two to six times the upper limits of normal) have been noted. In the majority of patients, renal function has remained normal.

The severity of illness might be highly variable, ranging from mild illness to death. Although a few close contacts of patients with SARS have developed a similar illness, the majority have remained well. Some close contacts have reported a mild, febrile illness without respiratory signs or symptoms, suggesting the illness might not always progress to the respiratory phase.

Treatment regimens have included several antibiotics to presumptively treat known bacterial agents of atypical pneumonia. In several locations, therapy also has included antiviral agents such as oseltamivir or ribavirin. Steroids have also been administered orally or intravenously to patients in combination with ribavirin and other antimicrobials. At present, the most efficacious treatment regimen, if any, is unknown.

The causative agent of SARS appears to be a novel coronavirus that was isolated from patients who met the case definition of SARS (see Ksiazek et al., 2003, New England Journal of Medicine, 10.1056/NEJMoa030781. Indirect fluorescent antibody tests and enzyme-linked immunosorbent assays made with the new coronavirus isolate have been used to demonstrate a virus-specific serologic response. Amplification of short regions of the polymerase gene, (the most strongly conserved part of the Coronavirus genome) by reverse transcriptase polymerase chain reaction (RT-PCR) and nucleotide sequencing revealed that the SARS virus is a novel Coronavirus which has not previously been present in human populations. This conclusion is confirmed by serological (antigenic) investigations. The sequence of the SARS associated coronavirus was recently made available through the CDC.

Viral entry into cells occurs via endocytosis and membrane fusion. Replication occurs in the cytoplasm. Initially, the 5' 20kb of the (+)sense genome is translated to produce a viral polymerase, which then produces a full-length (-)sense strand. This is used as a template to produce mRNA as a nested set of transcripts, all with an identical 5' non-translated leader sequence of 72nt and coincident 3' polyadenylated ends. Each mRNA is monocistronic, the genes at the 5' end being translated from the longest mRNA. These unusual cytoplasmic structures are produced not by splicing but by the polymerase during transcription. Between each of the genes there is a repeated intergenic sequence - UCUAAAC - which interacts with the transcriptase plus cellular factors to splice the leader sequence onto the start of each ORF. Viral assembly occurs by budding

into the golgi apparatus, and viral particles are transported to the surface of the cell and are subsequently released.

The SARS virus can be grown in Vero cells (a fibroblast cell line isolated in 1962 from a primate). This is a novel property for human cornaviruses which usually cannot be cultivated. In these cells, virus infection results in a cytopathic effect, and budding of Coronavirus-like particles from the endoplasmic reticulum within infected cells.

Detection of the SARS virus can be accomplished with serological testing and molecular diagnotic procedures. Serological testing for anti-Coronavirus antibodies consists of indirect fluorescent antibody testing and enzyme-linked immunosorbent assays (ELISA) which detect antibodies against the virus produced in response to infection. Molecular testing consists of reverse transcriptase-polymerase chain reaction (RT-PCR) tests specific for the RNA from the novel Coronavirus.

The use of small interfering nucleic acid molecules targeting SARS genes therefore provides a class of novel therapeutic agents that can be used in the treatment and diagnosis of SARS virus infection, acute respiratory failure, viral pneumonia, or any other disease or condition that responds to modulation of SARS genes.

Examples:

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

Example 1: Tandem synthesis of siNA constructs

Exemplary siNA molecules of the invention are synthesized in tandem using a cleavable linker, for example, a succinyl-based linker. Tandem synthesis as described herein is followed by a one-step purification process that provides RNAi molecules in high yield. This approach is highly amenable to siNA synthesis in support of high throughput RNAi screening, and can be readily adapted to multi-column or multi-well synthesis platforms.

After completing a tandem synthesis of a siNA oligo and its complement in which the 5'-terminal dimethoxytrityl (5'-O-DMT) group remains intact (trityl on synthesis), the

oligonucleotides are deprotected as described above. Following deprotection, the siNA sequence strands are allowed to spontaneously hybridize. This hybridization yields a duplex in which one strand has retained the 5'-O-DMT group while the complementary strand comprises a terminal 5'-hydroxyl. The newly formed duplex behaves as a single molecule during routine solid-phase extraction purification (Trityl-On purification) even though only one molecule has a dimethoxytrityl group. Because the strands form a stable duplex, this dimethoxytrityl group (or an equivalent group, such as other trityl groups or other hydrophobic moieties) is all that is required to purify the pair of oligos, for example, by using a C18 cartridge.

Standard phosphoramidite synthesis chemistry is used up to the point of introducing a tandem linker, such as an inverted deoxy abasic succinate or glyceryl succinate linker (see **Figure 1**) or an equivalent cleavable linker. A non-limiting example of linker coupling conditions that can be used includes a hindered base such as diisopropylethylamine (DIPA) and/or DMAP in the presence of an activator reagent such as Bromotripyrrolidinophosphoniumhexaflurorophosphate (PyBrOP). After the linker is coupled, standard synthesis chemistry is utilized to complete synthesis of the second sequence leaving the terminal the 5'-O-DMT intact. Following synthesis, the resulting oligonucleotide is deprotected according to the procedures described herein and quenched with a suitable buffer, for example with 50mM NaOAc or 1.5M $NH_4H_2CO_3$.

Purification of the siNA duplex can be readily accomplished using solid phase extraction, for example using a Waters C18 SepPak 1g cartridge conditioned with 1 column volume (CV) of acetonitrile, 2 CV H2O, and 2 CV 50mM NaOAc. The sample is loaded and then washed with 1 CV H2O or 50mM NaOAc. Failure sequences are eluted with 1 CV 14% ACN (Aqueous with 50mM NaOAc and 50mM NaCl). The column is then washed, for example with 1 CV H2O followed by on-column detritylation, for example by passing 1 CV of 1% aqueous trifluoroacetic acid (TFA) over the column, then adding a second CV of 1% aqueous TFA to the column and allowing to stand for approximately 10 minutes. The remaining TFA solution is removed and the column washed with H20 followed by 1 CV 1M NaCl and additional H2O. The siNA duplex product is then eluted, for example, using 1 CV 20% aqueous CAN.

Figure 2 provides an example of MALDI-TOF mass spectrometry analysis of a purified siNA construct in which each peak corresponds to the calculated mass of an individual siNA strand of the siNA duplex. The same purified siNA provides three peaks when analyzed by capillary gel electrophoresis (CGE), one peak presumably corresponding to the duplex siNA, and two peaks presumably corresponding to the separate siNA sequence strands. Ion exchange HPLC analysis of the same siNA contract only shows a single peak. Testing of the purified siNA construct using a luciferase reporter assay described below demonstrated the same RNAi activity compared to siNA constructs generated from separately synthesized oligonucleotide sequence strands.

<u>Example 2: Identification of potential siNA target sites in any RNA sequence</u>

The sequence of an RNA target of interest, such as a viral or human mRNA transcript, is screened for target sites, for example by using a computer folding algorithm. In a non-limiting example, the sequence of a gene or RNA gene transcript derived from a database, such as Genbank, is used to generate siNA targets having complementarity to the target. Such sequences can be obtained from a database, or can be determined experimentally as known in the art. Target sites that are known, for example, those target sites determined to be effective target sites based on studies with other nucleic acid molecules, for example ribozymes or antisense, or those targets known to be associated with a disease or condition such as those sites containing mutations or deletions, can be used to design siNA molecules targeting those sites. Various parameters can be used to determine which sites are the most suitable target sites within the target RNA sequence. These parameters include but are not limited to secondary or tertiary RNA structure, the nucleotide base composition of the target sequence, the degree of homology between various regions of the target sequence, or the relative position of the target sequence within the RNA transcript. Based on these determinations, any number of target sites within the RNA transcript can be chosen to screen siNA molecules for efficacy, for example by using *in vitro* RNA cleavage assays, cell culture, or animal models. In a non-limiting example, anywhere from 1 to 1000 target sites are chosen within the transcript based on the size of the siNA construct to be used. High throughput screening assays can be developed for screening siNA molecules

using methods known in the art, such as with multi-well or multi-plate assays to determine efficient reduction in target gene expression.

Example 3: Selection of siNA molecule target sites in a RNA

The following non-limiting steps can be used to carry out the selection of siNAs targeting a given gene sequence or transcript.

1. The target sequence is parsed *in silico* into a list of all fragments or subsequences of a particular length, for example 23 nucleotide fragments, contained within the target sequence. This step is typically carried out using a custom Perl script, but commercial sequence analysis programs such as Oligo, MacVector, or the GCG Wisconsin Package can be employed as well.

2. In some instances the siNAs correspond to more than one target sequence; such would be the case for example in targeting different transcripts of the same gene, targeting different transcripts of more than one gene, or for targeting both the human gene and an animal homolog. In this case, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find matching sequences in each list. The subsequences are then ranked according to the number of target sequences that contain the given subsequence; the goal is to find subsequences that are present in most or all of the target sequences. Alternately, the ranking can identify subsequences that are unique to a target sequence, such as a mutant target sequence. Such an approach would enable the use of siNA to target specifically the mutant sequence and not effect the expression of the normal sequence.

3. In some instances the siNA subsequences are absent in one or more sequences while present in the desired target sequence; such would be the case if the siNA targets a gene with a paralogous family member that is to remain untargeted. As in case 2 above, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find sequences that are present in the target gene but are absent in the untargeted paralog.

4. The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.

5. The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.

6. The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.

7. The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.

8. Four or five target sites are chosen from the ranked list of subsequences as described above. For example, in subsequences having 23 nucleotides, the right 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the upper (sense) strand of the siNA duplex, while the reverse complement of the left 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the lower (antisense) strand of the siNA duplex (see **Tables II and III**). If terminal TT residues are desired for the sequence (as described in paragraph 7), then the two 3' terminal nucleotides of both the sense and antisense strands are replaced by TT prior to synthesizing the oligos.

9. The siNA molecules are screened in an *in vitro*, cell culture or animal model system to identify the most active siNA molecule or the most preferred target site within the target RNA sequence.

10. Other design considerations can be used when selecting target nucleic acid sequences, see for example Reynolds *et al.*, 2004, *Nature Biotechnology Advanced Online Publication*, 1 February 2004, doi:10.1038/nbt936 and Ui-Tei et al., 2004, Nucleic Acids Research, 32, doi:10.1093/nar/gkh247.

In an alternate approach, a pool of siNA constructs specific to a SARS target sequence is used to screen for target sites in cells expressing SARS RNA, such as VERO cells and/or FRhk-4 cells. The general strategy used in this approach is shown in **Figure 9.** A non-limiting example of such is a pool comprising sequences having SEQ ID NOs: 1-3392. Cells expressing SARS (e.g., VERO cells and/or FRhk-4 cells) are transfected with the pool of siNA constructs and cells that demonstrate a phenotype associated with SARS inhibition are sorted. The pool of siNA constructs can be expressed from transcription cassettes inserted into appropriate vectors (see for example **Figure 7** and **Figure 8**). The siNA from cells demonstrating a positive phenotypic change (e.g., decreased proliferation, decreased SARS mRNA levels or decreased SARS protein expression), are sequenced to determine the most suitable target site(s) within the target SARS RNA sequence.

Example 4: SARS targeted siNA design

siNA target sites were chosen by analyzing sequences of the SARS RNA target and optionally prioritizing the target sites on the basis of folding (structure of any given sequence analyzed to determine siNA accessibility to the target), by using a library of siNA molecules as described in Example 3, or alternately by using an *in vitro* siNA system as described in Example 6 herein. siNA molecules were designed that could bind each target and are optionally individually analyzed by computer folding to assess whether the siNA molecule can interact with the target sequence. Varying the length of the siNA molecules can be chosen to optimize activity. Generally, a sufficient number of complementary nucleotide bases are chosen to bind to, or otherwise interact with, the target RNA, but the degree of complementarity can be modulated to accommodate siNA duplexes or varying length or base composition. By using such methodologies, siNA molecules can be designed to target sites within any known RNA sequence, for example those RNA sequences corresponding to the any gene transcript.

Chemically modified siNA constructs are designed to provide nuclease stability for systemic administration in vivo and/or improved pharmacokinetic, localization, and delivery properties while preserving the ability to mediate RNAi activity. Chemical modifications as described herein are introduced synthetically using synthetic methods described herein and those generally known in the art. The synthetic siNA constructs are then assayed for nuclease stability in serum and/or cellular/tissue extracts (e.g. liver extracts). The synthetic siNA constructs are also tested in parallel for RNAi activity using an appropriate assay, such as a luciferase reporter assay as described herein or another suitable assay that can quantity RNAi activity. Synthetic siNA constructs that possess both nuclease stability and RNAi activity can be further modified and re-evaluated in stability and activity assays. The chemical modifications of the stabilized active siNA constructs can then be applied to any siNA sequence targeting any chosen RNA and used, for example, in target screening assays to pick lead siNA compounds for therapeutic development (see for example **Figure 11**).

Example 5: Chemical Synthesis and Purification of siNA

siNA molecules can be designed to interact with various sites in the RNA message, for example, target sequences within the RNA sequences described herein. The sequence of one strand of the siNA molecule(s) is complementary to the target site sequences described above. The siNA molecules can be chemically synthesized using methods described herein. Inactive siNA molecules that are used as control sequences can be synthesized by scrambling the sequence of the siNA molecules such that it is not complementary to the target sequence. Generally, siNA constructs can by synthesized using solid phase oligonucleotide synthesis methods as described herein (see for example Usman *et al.*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,117,657; 6,353,098; 6,362,323; 6,437,117; 6,469,158; Scaringe *et al.*, US Patent Nos. 6,111,086; 6,008,400; 6,111,086 all incorporated by reference herein in their entirety).

In a non-limiting example, RNA oligonucleotides are synthesized in a stepwise fashion using the phosphoramidite chemistry as is known in the art. Standard phosphoramidite chemistry involves the use of nucleosides comprising any of 5'-O-dimethoxytrityl, 2'-O-tert-butyldimethylsilyl, 3'-O-2-Cyanoethyl N,N-diisopropylphos-phoroamidite groups, and exocyclic amine protecting groups (e.g. N6-benzoyl adenosine,

N4 acetyl cytidine, and N2-isobutyryl guanosine). Alternately, 2′-O-Silyl Ethers can be used in conjunction with acid-labile 2′-O-orthoester protecting groups in the synthesis of RNA as described by Scaringe *supra*. Differing 2' chemistries can require different protecting groups, for example 2'-deoxy-2'-amino nucleosides can utilize N-phthaloyl protection as described by Usman *et al.*, US Patent 5,631,360, incorporated by reference herein in its entirety).

During solid phase synthesis, each nucleotide is added sequentially (3′- to 5′-direction) to the solid support-bound oligonucleotide. The first nucleoside at the 3′-end of the chain is covalently attached to a solid support (e.g., controlled pore glass or polystyrene) using various linkers. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are combined resulting in the coupling of the second nucleoside phosphoramidite onto the 5′-end of the first nucleoside. The support is then washed and any unreacted 5′-hydroxyl groups are capped with a capping reagent such as acetic anhydride to yield inactive 5′-acetyl moieties. The trivalent phosphorus linkage is then oxidized to a more stable phosphate linkage. At the end of the nucleotide addition cycle, the 5′-O-protecting group is cleaved under suitable conditions (e.g., acidic conditions for trityl-based groups and Fluoride for silyl-based groups). The cycle is repeated for each subsequent nucleotide.

Modification of synthesis conditions can be used to optimize coupling efficiency, for example by using differing coupling times, differing reagent/phosphoramidite concentrations, differing contact times, differing solid supports and solid support linker chemistries depending on the particular chemical composition of the siNA to be synthesized. Deprotection and purification of the siNA can be performed as is generally described in Deprotection and purification of the siNA can be performed as is generally described in Usman *et al.*, US 5,831,071, US 6,353,098, US 6,437,117, and Bellon *et al.*, US 6,054,576, US 6,162,909, US 6,303,773, or Scaringe *supra*, incorporated by reference herein in their entireties. Additionally, deprotection conditions can be modified to provide the best possible yield and purity of siNA constructs. For example, applicant has observed that oligonucleotides comprising 2'-deoxy-2'-fluoro nucleotides can degrade under inappropriate deprotection conditions. Such oligonucleotides are deprotected using aqueous methylamine at about 35°C for 30 minutes. If the 2'-deoxy-

2'-fluoro containing oligonucleotide also comprises ribonucleotides, after deprotection with aqueous methylamine at about 35°C for 30 minutes, TEA-HF is added and the reaction maintained at about 65°C for an additional 15 minutes.

Example 6: RNAi *in vitro* assay to assess siNA activity

An *in vitro* assay that recapitulates RNAi in a cell-free system is used to evaluate siNA constructs targeting SARS RNA targets. The assay comprises the system described by Tuschl *et al.*, 1999, *Genes and Development*, 13, 3191-3197 and Zamore *et al.*, 2000, *Cell*, 101, 25-33 adapted for use with SARS target RNA. A Drosophila extract derived from syncytial blastoderm is used to reconstitute RNAi activity *in vitro*. Target RNA is generated via *in vitro* transcription from an appropriate SARS expressing plasmid using T7 RNA polymerase or via chemical synthesis as described herein. Sense and antisense siNA strands (for example 20 uM each) are annealed by incubation in buffer (such as 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4, 2 mM magnesium acetate) for 1 minute at 90°C followed by 1 hour at 37°C , then diluted in lysis buffer (for example 100 mM potassium acetate, 30 mM HEPES-KOH at pH 7.4, 2mM magnesium acetate). Annealing can be monitored by gel electrophoresis on an agarose gel in TBE buffer and stained with ethidium bromide. The Drosophila lysate is prepared using zero to two-hour-old embryos from Oregon R flies collected on yeasted molasses agar that are dechorionated and lysed. The lysate is centrifuged and the supernatant isolated. The assay comprises a reaction mixture containing 50% lysate [vol/vol], RNA (10-50 pM final concentration), and 10% [vol/vol] lysis buffer containing siNA (10 nM final concentration). The reaction mixture also contains 10 mM creatine phosphate, 10 ug.ml creatine phosphokinase, 100 um GTP, 100 uM UTP, 100 uM CTP, 500 uM ATP, 5 mM DTT, 0.1 U/uL RNasin (Promega), and 100 uM of each amino acid. The final concentration of potassium acetate is adjusted to 100 mM. The reactions are pre-assembled on ice and preincubated at 25° C for 10 minutes before adding RNA, then incubated at 25° C for an additional 60 minutes. Reactions are quenched with 4 volumes of 1.25 x Passive Lysis Buffer (Promega). Target RNA cleavage is assayed by RT-PCR analysis or other methods known in the art and are compared to control reactions in which siNA is omitted from the reaction.

Alternately, internally-labeled target RNA for the assay is prepared by *in vitro* transcription in the presence of [alpha-^{32}p] CTP, passed over a G 50 Sephadex column by spin chromatography and used as target RNA without further purification. Optionally, target RNA is 5'-^{32}P-end labeled using T4 polynucleotide kinase enzyme. Assays are performed as described above and target RNA and the specific RNA cleavage products generated by RNAi are visualized on an autoradiograph of a gel. The percentage of cleavage is determined by PHOSPHOR IMAGER® (autoradiography) quantitation of bands representing intact control RNA or RNA from control reactions without siNA and the cleavage products generated by the assay.

In one embodiment, this assay is used to determine target sites the SARS RNA target for siNA mediated RNAi cleavage, wherein a plurality of siNA constructs are screened for RNAi mediated cleavage of the SARS RNA target, for example, by analyzing the assay reaction by electrophoresis of labeled target RNA, or by northern blotting, as well as by other methodology well known in the art.

Example 7: Nucleic acid inhibition of SARS target RNA *in vitro*

siNA molecules targeted to the human SARS RNA are designed and synthesized as described above. These nucleic acid molecules can be tested for cleavage activity *in vivo*, for example, using the following procedure. The target sequences and the nucleotide location within the SARS RNA are given in **Table II and III**.

Two formats are used to test the efficacy of siNAs targeting SARS. First, the reagents are tested in cell culture using, for example, VERO cells and/or FRhk-4 cells, to determine the extent of RNA and protein inhibition. siNA reagents (*e.g.*; see **Tables II and III**) are selected against the SARS target as described herein. RNA inhibition is measured after delivery of these reagents by a suitable transfection agent to, for example, VERO cells and/or FRhk-4 cells. Relative amounts of target RNA are measured versus actin using real-time PCR monitoring of amplification (*eg*., ABI 7700 TAQMAN®). A comparison is made to a mixture of oligonucleotide sequences made to unrelated targets or to a randomized siNA control with the same overall length and chemistry, but randomly substituted at each position. Primary and secondary lead reagents are chosen for the target and optimization performed. After an optimal transfection agent

concentration is chosen, a RNA time-course of inhibition is performed with the lead siNA molecule. In addition, a cell-plating format can be used to determine RNA inhibition.

Delivery of siNA to Cells

Cells (e.g., VERO cells and/or FRhk-4 cells infected with the SARS virus) are seeded, for example, at $1x10^5$ cells per well of a six-well dish in EGM-2 (BioWhittaker) the day before transfection. siNA (final concentration, for example 20nM) and cationic lipid (e.g., final concentration 2µg/ml) are complexed in EGM basal media (Bio Whittaker) at 37°C for 30 minutes in polystyrene tubes. Following vortexing, the complexed siNA is added to each well and incubated for the times indicated. For initial optimization experiments, cells are seeded, for example, at $1x10^3$ in 96 well plates and siNA complex added as described. Efficiency of delivery of siNA to cells is determined using a fluorescent siNA complexed with lipid. Cells in 6-well dishes are incubated with siNA for 24 hours, rinsed with PBS and fixed in 2% paraformaldehyde for 15 minutes at room temperature. Uptake of siNA is visualized using a fluorescent microscope.

TAQMAN® (real-time PCR monitoring of amplification) and Lightcycler quantification of mRNA

Total RNA is prepared from cells following siNA delivery, for example, using Qiagen RNA purification kits for 6-well or Rneasy extraction kits for 96-well assays. For TAQMAN® analysis (real-time PCR monitoring of amplification), dual-labeled probes are synthesized with the reporter dye, FAM or JOE, covalently linked at the 5'-end and the quencher dye TAMRA conjugated to the 3'-end. One-step RT-PCR amplifications are performed on, for example, an ABI PRISM 7700 Sequence Detector using 50 µl reactions consisting of 10 µl total RNA, 100 nM forward primer, 900 nM reverse primer, 100 nM probe, 1X TAQMAN® PCR reaction buffer (PE-Applied Biosystems), 5.5 mM $MgCl_2$, 300 µM each dATP, dCTP, dGTP, and dTTP, 10U RNase Inhibitor (Promega), 1.25U AMPLITAQ GOLD® (DNA polymerase) (PE-Applied Biosystems) and 10U M-MLV Reverse Transcriptase (Promega). The thermal cycling conditions can consist of 30 minutes at 48°C, 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C and 1 minute at 60°C. Quantitation of mRNA levels is determined relative to standards

generated from serially diluted total cellular RNA (300, 100, 33, 11 ng/rxn) and normalizing to ß-actin or GAPDH mRNA in parallel TAQMAN® reactions (real-time PCR monitoring of amplification). For each gene of interest an upper and lower primer and a fluorescently labeled probe are designed. Real time incorporation of SYBR Green I dye into a specific PCR product can be measured in glass capillary tubes using a lightcyler. A standard curve is generated for each primer pair using control cRNA. Values are represented as relative expression to GAPDH in each sample.

Western blotting

Nuclear extracts can be prepared using a standard micro preparation technique (see for example Andrews and Faller, 1991, *Nucleic Acids Research,* 19, 2499). Protein extracts from supernatants are prepared, for example using TCA precipitation. An equal volume of 20% TCA is added to the cell supernatant, incubated on ice for 1 hour and pelleted by centrifugation for 5 minutes. Pellets are washed in acetone, dried and resuspended in water. Cellular protein extracts are run on a 10% Bis-Tris NuPage (nuclear extracts) or 4-12% Tris-Glycine (supernatant extracts) polyacrylamide gel and transferred onto nitro-cellulose membranes. Non-specific binding can be blocked by incubation, for example, with 5% non-fat milk for 1 hour followed by primary antibody for 16 hour at 4°C. Following washes, the secondary antibody is applied, for example (1:10,000 dilution) for 1 hour at room temperature and the signal detected with SuperSignal reagent (Pierce).

Example 8: RNAi mediated inhibition of SARS RNA expression

siNA constructs (e.g., siNA constructs shown in **Table III**) are tested for efficacy in reducing SARS RNA expression in, for example, VERO cells and/or FRhk-4 cells. Cells are plated approximately 24h before transfection in 96-well plates at 5,000-7,500 cells/well, 100 µl/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50 µl/well and incubated for 20 minutes at room temperature. The siNA transfection mixtures are added to cells to give a final siNA concentration of 25 nM in a volume of 150 µl. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the

continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene and for a control gene (36B4, an RNA polymerase subunit) for normalization. The triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

In a non-limiting example, a siNA construct comprising ribonucleotides and 3'-terminal dithymidine caps is assayed along with a chemically modified siNA construct comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides and purine ribonucleotides in which the sense strand of the siNA is further modified with 5' and 3'-terminal inverted deoxyabasic caps and the antisense strand comprises a 3'-terminal phosphorothioate internucleotide linkage. Additional stabilization chemistries as described in Table IV are similarly assayed for activity. These siNA constructs are compared to appropriate matched chemistry inverted controls. In addition, the siNA constructs are also compared to untreated cells, cells transfected with lipid and scrambled siNA constructs, and cells transfected with lipid alone (transfection control).

Example 9: Animal Models

Evaluating the efficacy of anti-SARS agents in animal models is an important prerequisite to human clinical trials. Byron *et al.*, 2003, *Nature,* 425, 915, describe ferret and feline animal models of SARS virus infection. Haagmans et al., 2004, Nature Medicine, 10, 290-293, describe the use of pegylated interferon-alpha in protecting type 1 pneumocytes against SARS coronavirus infection in macaques. Gao *et al.,* 2003, *Lancet*, 362, 1895-6, describe the use of a SARS virus vaccine in monkeys. All of these models can be adapted for use for pre-clinical evaluation of the efficacy of nucleic acid compositions of the invetention in modulating SARS virus gene expression toward therapeutic use.

Example 10: Indications

The present body of knowledge in SARS research indicates the need for methods to assay SARS activity and for compounds that can regulate SARS expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related of SARS levels. In addition, the nucleic acid molecules can be used to treat disease state related to SARS levels.

Particular degenerative and disease states that can be associated with SARS expression modulation include, but are not limited to, SARS virus infection, liver failure, hepatocellular carcinoma, cirrhosis, and/or other disease states associated with SARS virus infection.

Immunomodulators, steroids, and anti-vrial compounds are non-limiting examples of pharmaceutical agents that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* siNA molecules) of the instant invention. The use of ribavirin and oseltamivir are non-limiting examples of chemotherapeutic agents that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* siNA molecules) of the instant invention. Those skilled in the art will recognize that other anti-cancer compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (*e.g.* siNA molecules) and are hence within the scope of the instant invention.

Example 11: Interferons

Interferons represent a non-limiting example of a class of compounds that can be used in conjuction with the siNA molecules of the invention for treating the diseases and/or conditions described herein. Type I interferons (IFN) are a class of natural cytokines that includes a family of greater than 25 IFN-α (Pesta, 1986, *Methods Enzymol.* 119, 3-14) as well as IFN-β, and IFN-ω. Although evolutionarily derived from the same gene (Diaz *et al.*, 1994, *Genomics* 22, 540-552), there are many differences in the primary sequence of these molecules, implying an evolutionary divergence in biologic activity. All type I IFN share a common pattern of biologic effects that begin with binding of the IFN to the cell surface receptor (Pfeffer & Strulovici, 1992, Transmembrane secondary messengers for IFN-α/β. In: *Interferon. Principles and*

Medical Applications., S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tyring, eds. 151-160). Binding is followed by activation of tyrosine kinases, including the Janus tyrosine kinases and the STAT proteins, which leads to the production of several IFN-stimulated gene products (Johnson *et al.*, 1994, *Sci. Am.* 270, 68-75). The IFN-stimulated gene products are responsible for the pleotropic biologic effects of type I IFN, including antiviral, antiproliferative, and immunomodulatory effects, cytokine induction, and HLA class I and class II regulation (Pestka *et al.*, 1987, *Annu. Rev. Biochem* 56, 727). Examples of IFN-stimulated gene products include 2-5-oligoadenylate synthetase (2-5 OAS), β_2-microglobulin, neopterin, p68 kinases, and the Mx protein (Chebath & Revel, 1992, The 2-5 A system: 2-5 A synthetase, isospecies and functions. In: *Interferon. Principles and Medical Applications,* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Jr. Fleischmann, T.K. Jr Hughes, G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tyring, eds., pp. 225-236; Samuel, 1992, The RNA-dependent P1/eIF-2α protein kinase. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tyring, eds. 237-250; Horisberger, 1992, MX protein: function and Mechanism of Action. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tyring, eds. 215-224). Although all type I IFN have similar biologic effects, not all the activities are shared by each type I IFN, and in many cases, the extent of activity varies quite substantially for each IFN subtype (Fish *et al*, 1989, *J. Interferon Res.* 9, 97-114; Ozes *et al.*, 1992, *J. Interferon Res.* 12, 55-59). More specifically, investigations into the properties of different subtypes of IFN-α and molecular hybrids of IFN-α have shown differences in pharmacologic properties (Rubinstein, 1987, *J. Interferon Res.* 7, 545-551). These pharmacologic differences can arise from as few as three amino acid residue changes (Lee *et al.*, 1982, *Cancer Res.* 42, 1312-1316).

Eighty-five to 166 amino acids are conserved in the known IFN-α subtypes. Excluding the IFN-α pseudogenes, there are approximately 25 known distinct IFN-α subtypes. Pairwise comparisons of these nonallelic subtypes show primary sequence

differences ranging from 2% to 23%. In addition to the naturally occurring IFNs, a non-natural recombinant type I interferon known as consensus interferon (CIFN) has been synthesized as a therapeutic compound (Tong *et al.*, 1997, *Hepatology* 26, 747-754).

Interferon is currently in use for at least 12 different indications, including infectious and autoimmune diseases and cancer (Borden, 1992, *N. Engl. J. Med.* 326, 1491-1492). For autoimmune diseases, IFN has been utilized for treatment of rheumatoid arthritis, multiple sclerosis, and Crohn's disease. For treatment of cancer, IFN has been used alone or in combination with a number of different compounds. Specific types of cancers for which IFN has been used include squamous cell carcinomas, melanomas, hypernephromas, hemangiomas, hairy cell leukemia, and Kaposi's sarcoma. In the treatment of infectious diseases, IFNs increase the phagocytic activity of macrophages and cytotoxicity of lymphocytes and inhibits the propagation of cellular pathogens. Specific indications for which IFN has been used as treatment include hepatitis B, human papillomavirus types 6 and 11 (i.e. genital warts) (Leventhal *et al.*, 1991, *N Engl J Med* 325, 613-617), chronic granulomatous disease, and SARS virus.

Pegylated interferons, i.e., interferons conjugated with polyethylene glycol (PEG), have demonstrated improved characteristics over interferon. Advantages incurred by PEG conjugation can include an improved pharmacokinetic profile compared to interferons lacking PEG, thus imparting more convenient dosing regimes, improved tolerance, and improved antiviral efficacy. Such improvements have been demonstrated in clinical studies of both polyethylene glycol interferon alfa-2a (PEGASYS, Roche) and polyethylene glycol interferon alfa-2b (VIRAFERON PEG, PEG-INTRON, Enzon/Schering Plough).

siNA molecules in combination with interferons and polyethylene glycol interferons have the potential to improve the effectiveness of treatment of SARS or any of the other indications discussed above. siNA molecules targeting RNAs associated with SARS virus infection can be used individually or in combination with other therapies such as interferons and polyethylene glycol interferons and to achieve enhanced efficacy.

Example 12: Diagnostic uses

The siNA molecules of the invention can be used in a variety of diagnostic applications, such as in the identification of molecular targets (e.g., RNA) in a variety of applications, for example, in clinical, industrial, environmental, agricultural and/or research settings. Such diagnostic use of siNA molecules involves utilizing reconstituted RNAi systems, for example, using cellular lysates or partially purified cellular lysates. siNA molecules of this invention can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of endogenous or exogenous, for example viral, RNA in a cell. The close relationship between siNA activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple siNA molecules described in this invention, one can map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with siNA molecules can be used to inhibit gene expression and define the role of specified gene products in the progression of disease or infection. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes, siNA molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations siNA molecules and/or other chemical or biological molecules). Other *in vitro* uses of siNA molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with a disease, infection, or related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a siNA using standard methodologies, for example, fluorescence resonance emission transfer (FRET).

In a specific example, siNA molecules that cleave only wild-type or mutant forms of the target RNA are used for the assay. The first siNA molecules (*i.e.*, those that cleave only wild-type forms of target RNA) are used to identify wild-type RNA present in the sample and the second siNA molecules (*i.e.*, those that cleave only mutant forms of target RNA) are used to identify mutant RNA in the sample. As reaction controls,

synthetic substrates of both wild-type and mutant RNA are cleaved by both siNA molecules to demonstrate the relative siNA efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus, each analysis requires two siNA molecules, two substrates and one unknown sample, which is combined into six reactions. The presence of cleavage products is determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, disease related or infection related) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels is adequate and decreases the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims. The present invention teaches

one skilled in the art to test various combinations and/or substitutions of chemical modifications described herein toward generating nucleic acid constructs with improved activity for mediating RNAi activity. Such improved activity can comprise improved stability, improved bioavailability, and/or improved activation of cellular responses mediating RNAi. Therefore, the specific embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying siNA molecules with improved RNAi activity.

The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Table I: SARS virus Accession Numbers

LOCUS NC_004718 29736 bp ss-RNA linear VRL 15-APR-2003
DEFINITION SARS coronavirus, complete genome.
ACCESSION NC_004718

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Table II: SARS siNA and Target Sequences

SARS CoV NC_004718

Pos	Seq	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID
3	ACCCAGGAAAAGCCAACCA	1	3	ACCCAGGAAAAGCCAACCA	1	21	UGGUUGGCUUUUCCUGGGU	1652
21	AACCUCGAUCUCUUGUAGA	2	21	AACCUCGAUCUCUUGUAGA	2	39	UCUACAAGAGAUCGAGGUU	1653
39	AUCUGUUCUCUAAACGAAC	3	39	AUCUGUUCUCUAAACGAAC	3	57	GUUCGUUUAGAGAACAGAU	1654
57	CUUUAAAAUCUGUGUAGCU	4	57	CUUUAAAAUCUGUGUAGCU	4	75	AGCUACACAGAUUUUAAAG	1655
75	UGUCGCUCGGCUGCAUGCC	5	75	UGUCGCUCGGCUGCAUGCC	5	93	GGCAUGCAGCCGAGCGACA	1656
93	CUAGUGCACCUACGCAGUA	6	93	CUAGUGCACCUACGCAGUA	6	111	UACUGCGUAGGUGCACUAG	1657
111	AUAAACAAUAAUAAAUUUU	7	111	AUAAACAAUAAUAAAUUUU	7	129	AAAAUUUAUUAUUGUUUAU	1658
129	UACUGUCGUUGACAAGAAA	8	129	UACUGUCGUUGACAAGAAA	8	147	UUUCUUGUCAACGACAGUA	1659
147	ACGAGUAACUCGUCCCUCU	9	147	ACGAGUAACUCGUCCCUCU	9	165	AGAGGGACGAGUUACUCGU	1660
165	UUCUGCAGACUGCUUACGG	10	165	UUCUGCAGACUGCUUACGG	10	183	CCGUAAGCAGUCUGCAGAA	1661
183	GUUUCGUCCGUGUUGCAGU	11	183	GUUUCGUCCGUGUUGCAGU	11	201	ACUGCAACACGGACGAAAC	1662
201	UCGAUCAUCAGCAUACCUA	12	201	UCGAUCAUCAGCAUACCUA	12	219	UAGGUAUGCUGAUGAUCGA	1663
219	AGGUUUCGUCCGGGUGUGA	13	219	AGGUUUCGUCCGGGUGUGA	13	237	UCACACCCGGACGAAACCU	1664
237	ACCGAAAGGUAAGAUGGAG	14	237	ACCGAAAGGUAAGAUGGAG	14	255	CUCCAUCUUACCUUUCGGU	1665
255	GAGCCUUGUUCUUGGUGUC	15	255	GAGCCUUGUUCUUGGUGUC	15	273	GACACCAAGAACAAGGCUC	1666
273	CAACGAGAAAACACACGUC	16	273	CAACGAGAAAACACACGUC	16	291	GACGUGUGUUUUCUCGUUG	1667
291	CCAACUCAGUUUGCCUGUC	17	291	CCAACUCAGUUUGCCUGUC	17	309	GACAGGCAAACUGAGUUGG	1668
309	CCUUCAGGUUAGAGACGUG	18	309	CCUUCAGGUUAGAGACGUG	18	327	CACGUCUCUAACCUGAAGG	1669
327	GCUAGUGCGUGGCUUCGGG	19	327	GCUAGUGCGUGGCUUCGGG	19	345	CCCGAAGCCACGCACUAGC	1670
345	GGACUCUGUGGAAGAGGCC	20	345	GGACUCUGUGGAAGAGGCC	20	363	GGCCUCUUCCACAGAGUCC	1671
363	CCUAUCGGAGGCACGUGAA	21	363	CCUAUCGGAGGCACGUGAA	21	381	UUCACGUGCCUCCGAUAGG	1672
381	ACACCUCAAAAAUGGCACU	22	381	ACACCUCAAAAAUGGCACU	22	399	AGUGCCAUUUUUGAGGUGU	1673
399	UUGUGGUCUAGUAGAGCUG	23	399	UUGUGGUCUAGUAGAGCUG	23	417	CAGCUCUACUAGACCACAA	1674
417	GGAAAAAGGCGUACUGCCC	24	417	GGAAAAAGGCGUACUGCCC	24	435	GGGCAGUACGCCUUUUUCC	1675
435	CCAGCUUGAACAGCCCUAU	25	435	CCAGCUUGAACAGCCCUAU	25	453	AUAGGGCUGUUCAAGCUGG	1676
453	UGUGUUCAUUAAACGUUCU	26	453	UGUGUUCAUUAAACGUUCU	26	471	AGAACGUUUAAUGAACACA	1677
471	UGAUGCCUUAAGCACCAAU	27	471	UGAUGCCUUAAGCACCAAU	27	489	AUUGGUGCUUAAGGCAUCA	1678
489	UCACGGCCACAAGGUCGUU	28	489	UCACGGCCACAAGGUCGUU	28	507	AACGACCUUGUGGCCGUGA	1679
507	UGAGCUGGUUGCAGAAAUG	29	507	UGAGCUGGUUGCAGAAAUG	29	525	CAUUUCUGCAACCAGCUCA	1680
525	GGACGGCAUUCAGUACGGU	30	525	GGACGGCAUUCAGUACGGU	30	543	ACCGUACUGAAUGCCGUCC	1681
543	UCGUAGCGGUAUAACACUG	31	543	UCGUAGCGGUAUAACACUG	31	561	CAGUGUUAUACCGCUACGA	1682
561	GGGAGUACUCGUGCCACAU	32	561	GGGAGUACUCGUGCCACAU	32	579	AUGUGGCACGAGUACUCCC	1683
579	UGUGGGCGAAACCCCAAUU	33	579	UGUGGGCGAAACCCCAAUU	33	597	AAUUGGGGUUUCGCCCACA	1684
597	UGCAUACCGCAAUGUUCUU	34	597	UGCAUACCGCAAUGUUCUU	34	615	AAGAACAUUGCGGUAUGCA	1685
615	UCUUCGUAAGAACGGUAAU	35	615	UCUUCGUAAGAACGGUAAU	35	633	AUUACCGUUCUUACGAAGA	1686
633	UAAGGGAGCCGGUGGUCAU	36	633	UAAGGGAGCCGGUGGUCAU	36	651	AUGACCACCGGCUCCCUUA	1687

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651	UAGCUAUGGCAUCGAUCUA	37	651	UAGCUAUGGCAUCGAUCUA	37	669	UAGAUCGAUGCCAUAGCUA	1688
669	AAAGUCUUAUGACUUAGGU	38	669	AAAGUCUUAUGACUUAGGU	38	687	ACCUAAGUCAUAAGACUUU	1689
687	UGACGAGCUUGGCACUGAU	39	687	UGACGAGCUUGGCACUGAU	39	705	AUCAGUGCCAAGCUCGUCA	1690
705	UCCCAUUGAAGAUUAUGAA	40	705	UCCCAUUGAAGAUUAUGAA	40	723	UUCAUAAUCUUCAAUGGGA	1691
723	ACAAAACUGGAACACUAAG	41	723	ACAAAACUGGAACACUAAG	41	741	CUUAGUGUUCCAGUUUUGU	1692
741	GCAUGGCAGUGGUGCACUC	42	741	GCAUGGCAGUGGUGCACUC	42	759	GAGUGCACCACUGCCAUGC	1693
759	CCGUGAACUCACUCGUGAG	43	759	CCGUGAACUCACUCGUGAG	43	777	CUCACGAGUGAGUUCACGG	1694
777	GCUCAAUGGAGGUGCAGUC	44	777	GCUCAAUGGAGGUGCAGUC	44	795	GACUGCACCUCCAUUGAGC	1695
795	CACUCGCUAUGUCGACAAC	45	795	CACUCGCUAUGUCGACAAC	45	813	GUUGUCGACAUAGCGAGUG	1696
813	CAAUUUCUGUGGCCCAGAU	46	813	CAAUUUCUGUGGCCCAGAU	46	831	AUCUGGGCCACAGAAAUUG	1697
831	UGGGUACCCUCUUGAUUGC	47	831	UGGGUACCCUCUUGAUUGC	47	849	GCAAUCAAGAGGGUACCCA	1698
849	CAUCAAAGAUUUUCUCGCA	48	849	CAUCAAAGAUUUUCUCGCA	48	867	UGCGAGAAAAUCUUUGAUG	1699
867	ACGCGCGGGCAAGUCAAUG	49	867	ACGCGCGGGCAAGUCAAUG	49	885	CAUUGACUUGCCCGCGCGU	1700
885	GUGCACUCUUUCCGAACAA	50	885	GUGCACUCUUUCCGAACAA	50	903	UUGUUCGGAAAGAGUGCAC	1701
903	ACUUGAUUACAUCGAGUCG	51	903	ACUUGAUUACAUCGAGUCG	51	921	CGACUCGAUGUAAUCAAGU	1702
921	GAAGAGAGGUGUCUACUGC	52	921	GAAGAGAGGUGUCUACUGC	52	939	GCAGUAGACACCUCUCUUC	1703
939	CUGCCGUGACCAUGAGCAU	53	939	CUGCCGUGACCAUGAGCAU	53	957	AUGCUCAUGGUCACGGCAG	1704
957	UGAAAUUGCCUGGUUCACU	54	957	UGAAAUUGCCUGGUUCACU	54	975	AGUGAACCAGGCAAUUUCA	1705
975	UGAGCGCUCUGAUAAGAGC	55	975	UGAGCGCUCUGAUAAGAGC	55	993	GCUCUUAUCAGAGCGCUCA	1706
993	CUACGAGCACCAGACACCC	56	993	CUACGAGCACCAGACACCC	56	1011	GGGUGUCUGGUGCUCGUAG	1707
1011	CUUCGAAAUUAAGAGUGCC	57	1011	CUUCGAAAUUAAGAGUGCC	57	1029	GGCACUCUUAAUUUCGAAG	1708
1029	CAAGAAAUUUGACACUUUC	58	1029	CAAGAAAUUUGACACUUUC	58	1047	GAAAGUGUCAAAUUUCUUG	1709
1047	CAAAGGGGAAUGCCCAAAG	59	1047	CAAAGGGGAAUGCCCAAAG	59	1065	CUUUGGGCAUUCCCCUUUG	1710
1065	GUUUGUGUUUCCUCUUAAC	60	1065	GUUUGUGUUUCCUCUUAAC	60	1083	GUUAAGAGGAAACACAAAC	1711
1083	CUCAAAAGUCAAAGUCAUU	61	1083	CUCAAAAGUCAAAGUCAUU	61	1101	AAUGACUUUGACUUUUGAG	1712
1101	UCAACCACGUGUUGAAAAG	62	1101	UCAACCACGUGUUGAAAAG	62	1119	CUUUUCAACACGUGGUUGA	1713
1119	GAAAAAGACUGAGGGUUUC	63	1119	GAAAAAGACUGAGGGUUUC	63	1137	GAAACCCUCAGUCUUUUUC	1714
1137	CAUGGGGCGUAUACGCUCU	64	1137	CAUGGGGCGUAUACGCUCU	64	1155	AGAGCGUAUACGCCCCAUG	1715
1155	UGUGUACCCUGUUGCAUCU	65	1155	UGUGUACCCUGUUGCAUCU	65	1173	AGAUGCAACAGGGUACACA	1716
1173	UCCACAGGAGUGUAACAAU	66	1173	UCCACAGGAGUGUAACAAU	66	1191	AUUGUUACACUCCUGUGGA	1717
1191	UAUGCACUUGUCUACCUUG	67	1191	UAUGCACUUGUCUACCUUG	67	1209	CAAGGUAGACAAGUGCAUA	1718
1209	GAUGAAAUGUAAUCAUUGC	68	1209	GAUGAAAUGUAAUCAUUGC	68	1227	GCAAUGAUUACAUUUCAUC	1719
1227	CGAUGAAGUUUCAUGGCAG	69	1227	CGAUGAAGUUUCAUGGCAG	69	1245	CUGCCAUGAAACUUCAUCG	1720
1245	GACGUGCGACUUUCUGAAA	70	1245	GACGUGCGACUUUCUGAAA	70	1263	UUUCAGAAAGUCGCACGUC	1721
1263	AGCCACUUGUGAACAUUGU	71	1263	AGCCACUUGUGAACAUUGU	71	1281	ACAAUGUUCACAAGUGGCU	1722
1281	UGGCACUGAAAAUUUAGUU	72	1281	UGGCACUGAAAAUUUAGUU	72	1299	AACUAAAUUUUCAGUGCCA	1723
1299	UAUUGAAGGACCUACUACA	73	1299	UAUUGAAGGACCUACUACA	73	1317	UGUAGUAGGUCCUUCAAUA	1724
1317	AUGUGGGUACCUACCUACU	74	1317	AUGUGGGUACCUACCUACU	74	1335	AGUAGGUAGGUACCCACAU	1725
1335	UAAUGCUGUAGUGAAAAUG	75	1335	UAAUGCUGUAGUGAAAAUG	75	1353	CAUUUUCACUACAGCAUUA	1726
1353	GCCAUGUCCUGCCUGUCAA	76	1353	GCCAUGUCCUGCCUGUCAA	76	1371	UUGACAGGCAGGACAUGGC	1727
1371	AGACCCAGAGAUUGGACCU	77	1371	AGACCCAGAGAUUGGACCU	77	1389	AGGUCCAAUCUCUGGGUCU	1728
1389	UGAGCAUAGUGUUGCAGAU	78	1389	UGAGCAUAGUGUUGCAGAU	78	1407	AUCUGCAACACUAUGCUCA	1729

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1407	UUAUCACAACCACUCAAAC	79	1407	UUAUCACAACCACUCAAAC	79	1425	GUUUGAGUGGUUGUGAUAA	1730
1425	CAUUGAAACUCGACUCCGC	80	1425	CAUUGAAACUCGACUCCGC	80	1443	GCGGAGUCGAGUUUCAAUG	1731
1443	CAAGGGAGGUAGGACUAGA	81	1443	CAAGGGAGGUAGGACUAGA	81	1461	UCUAGUCCUACCUCCCUUG	1732
1461	AUGUUUUGGAGGCUGUGUG	82	1461	AUGUUUUGGAGGCUGUGUG	82	1479	CACACAGCCUCCAAAACAU	1733
1479	GUUUGCCUAUGUUGGCUGC	83	1479	GUUUGCCUAUGUUGGCUGC	83	1497	GCAGCCAACAUAGGCAAAC	1734
1497	CUAUAAUAAGCGUGCCUAC	84	1497	CUAUAAUAAGCGUGCCUAC	84	1515	GUAGGCACGCUUAUUAUAG	1735
1515	CUGGGUUCCUCGUGCUAGU	85	1515	CUGGGUUCCUCGUGCUAGU	85	1533	ACUAGCACGAGGAACCCAG	1736
1533	UGCUGAUAUUGGCUCAGGC	86	1533	UGCUGAUAUUGGCUCAGGC	86	1551	GCCUGAGCCAAUAUCAGCA	1737
1551	CCAUACUGGCAUUACUGGU	87	1551	CCAUACUGGCAUUACUGGU	87	1569	ACCAGUAAUGCCAGUAUGG	1738
1569	UGACAAUGUGGAGACCUUG	88	1569	UGACAAUGUGGAGACCUUG	88	1587	CAAGGUCUCCACAUUGUCA	1739
1587	GAAUGAGGAUCUCCUUGAG	89	1587	GAAUGAGGAUCUCCUUGAG	89	1605	CUCAAGGAGAUCCUCAUUC	1740
1605	GAUACUGAGUCGUGAACGU	90	1605	GAUACUGAGUCGUGAACGU	90	1623	ACGUUCACGACUCAGUAUC	1741
1623	UGUUAACAUUAACAUUGUU	91	1623	UGUUAACAUUAACAUUGUU	91	1641	AACAAUGUUAAUGUUAACA	1742
1641	UGGCGAUUUUCAUUUGAAU	92	1641	UGGCGAUUUUCAUUUGAAU	92	1659	AUUCAAAUGAAAAUCGCCA	1743
1659	UGAAGAGGUUGCCAUCAUU	93	1659	UGAAGAGGUUGCCAUCAUU	93	1677	AAUGAUGGCAACCUCUUCA	1744
1677	UUUGGCAUCUUUCUCUGCU	94	1677	UUUGGCAUCUUUCUCUGCU	94	1695	AGCAGAGAAAGAUGCCAAA	1745
1695	UUCUACAAGUGCCUUUAUU	95	1695	UUCUACAAGUGCCUUUAUU	95	1713	AAUAAAGGCACUUGUAGAA	1746
1713	UGACACUAUAAAGAGUCUU	96	1713	UGACACUAUAAAGAGUCUU	96	1731	AAGACUCUUUAUAGUGUCA	1747
1731	UGAUUACAAGUCUUUCAAA	97	1731	UGAUUACAAGUCUUUCAAA	97	1749	UUUGAAAGACUUGUAAUCA	1748
1749	AACCAUUGUUGAGUCCUGC	98	1749	AACCAUUGUUGAGUCCUGC	98	1767	GCAGGACUCAACAAUGGUU	1749
1767	CGGUAACUAUAAAGUUACC	99	1767	CGGUAACUAUAAAGUUACC	99	1785	GGUAACUUUAUAGUUACCG	1750
1785	CAAGGGAAAGCCCGUAAAA	100	1785	CAAGGGAAAGCCCGUAAAA	100	1803	UUUUACGGGCUUUCCCUUG	1751
1803	AGGUGCUUGGAACAUUGGA	101	1803	AGGUGCUUGGAACAUUGGA	101	1821	UCCAAUGUUCCAAGCACCU	1752
1821	ACAACAGAGAUCAGUUUUA	102	1821	ACAACAGAGAUCAGUUUUA	102	1839	UAAAACUGAUCUCUGUUGU	1753
1839	AACACCACUGUGUGGUUUU	103	1839	AACACCACUGUGUGGUUUU	103	1857	AAAACCACACAGUGGUGUU	1754
1857	UCCCUCACAGGCUGCUGGU	104	1857	UCCCUCACAGGCUGCUGGU	104	1875	ACCAGCAGCCUGUGAGGGA	1755
1875	UGUUAUCAGAUCAAUUUUU	105	1875	UGUUAUCAGAUCAAUUUUU	105	1893	AAAAAUUGAUCUGAUAACA	1756
1893	UGCGCGCACACUUGAUGCA	106	1893	UGCGCGCACACUUGAUGCA	106	1911	UGCAUCAAGUGUGCGCGCA	1757
1911	AGCAAACCACUCAAUUCCU	107	1911	AGCAAACCACUCAAUUCCU	107	1929	AGGAAUUGAGUGGUUUGCU	1758
1929	UGAUUUGCAAAGAGCAGCU	108	1929	UGAUUUGCAAAGAGCAGCU	108	1947	AGCUGCUCUUUGCAAAUCA	1759
1947	UGUCACCAUACUUGAUGGU	109	1947	UGUCACCAUACUUGAUGGU	109	1965	ACCAUCAAGUAUGGUGACA	1760
1965	UAUUUCUGAACAGUCAUUA	110	1965	UAUUUCUGAACAGUCAUUA	110	1983	UAAUGACUGUUCAGAAAUA	1761
1983	ACGUCUUGUCGACGCCAUG	111	1983	ACGUCUUGUCGACGCCAUG	111	2001	CAUGGCGUCGACAAGACGU	1762
2001	GGUUUAUACUUCAGACCUG	112	2001	GGUUUAUACUUCAGACCUG	112	2019	CAGGUCUGAAGUAUAAACC	1763
2019	GCUCACCAACAGUGUCAUU	113	2019	GCUCACCAACAGUGUCAUU	113	2037	AAUGACACUGUUGGUGAGC	1764
2037	UAUUAUGGCAUAUGUAACU	114	2037	UAUUAUGGCAUAUGUAACU	114	2055	AGUUACAUAUGCCAUAAUA	1765
2055	UGGUGGUCUUGUACAACAG	115	2055	UGGUGGUCUUGUACAACAG	115	2073	CUGUUGUACAAGACCACCA	1766
2073	GACUUCUCAGUGGUUGUCU	116	2073	GACUUCUCAGUGGUUGUCU	116	2091	AGACAACCACUGAGAAGUC	1767
2091	UAAUCUUUUGGCACUACU	117	2091	UAAUCUUUUGGCACUACU	117	2109	AGUAGUGCCCAAAAGAUUA	1768
2109	UGUUGAAAAACUCAGGCCU	118	2109	UGUUGAAAAACUCAGGCCU	118	2127	AGGCCUGAGUUUUUCAACA	1769
2127	UAUCUUUGAAUGGAUUGAG	119	2127	UAUCUUUGAAUGGAUUGAG	119	2145	CUCAAUCCAUUCAAAGAUA	1770
2145	GGCGAAACUUAGUGCAGGA	120	2145	GGCGAAACUUAGUGCAGGA	120	2163	UCCUGCACUAAGUUUCGCC	1771

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2163	AGUUGAAUUUCUCAAGGAU	121	2163	AGUUGAAUUUCUCAAGGAU	121	2181	AUCCUUGAGAAAUUCAACU	1772
2181	UGCUUGGGAGAUUCUCAAA	122	2181	UGCUUGGGAGAUUCUCAAA	122	2199	UUUGAGAAUCUCCCAAGCA	1773
2199	AUUUCUCAUUACAGGUGUU	123	2199	AUUUCUCAUUACAGGUGUU	123	2217	AACACCUGUAAUGAGAAAU	1774
2217	UUUUGACAUCGUCAAGGGU	124	2217	UUUUGACAUCGUCAAGGGU	124	2235	ACCCUUGACGAUGUCAAAA	1775
2235	UCAAAUACAGGUUGCUUCA	125	2235	UCAAAUACAGGUUGCUUCA	125	2253	UGAAGCAACCUGUAUUUGA	1776
2253	AGAUAACAUCAAGGAUUGU	126	2253	AGAUAACAUCAAGGAUUGU	126	2271	ACAAUCCUUGAUGUUAUCU	1777
2271	UGUAAAAUGCUUCAUUGAU	127	2271	UGUAAAAUGCUUCAUUGAU	127	2289	AUCAAUGAAGCAUUUUACA	1778
2289	UGUUGUUAACAAGGCACUC	128	2289	UGUUGUUAACAAGGCACUC	128	2307	GAGUGCCUUGUUAACAACA	1779
2307	CGAAAUGUGCAUUGAUCAA	129	2307	CGAAAUGUGCAUUGAUCAA	129	2325	UUGAUCAAUGCACAUUUCG	1780
2325	AGUCACUAUCGCUGGCGCA	130	2325	AGUCACUAUCGCUGGCGCA	130	2343	UGCGCCAGCGAUAGUGACU	1781
2343	AAAGUUGCGAUCACUCAAC	131	2343	AAAGUUGCGAUCACUCAAC	131	2361	GUUGAGUGAUCGCAACUUU	1782
2361	CUUAGGUGAAGUCUUCAUC	132	2361	CUUAGGUGAAGUCUUCAUC	132	2379	GAUGAAGACUUCACCUAAG	1783
2379	CGCUCAAAGCAAGGGACUU	133	2379	CGCUCAAAGCAAGGGACUU	133	2397	AAGUCCCUUGCUUUGAGCG	1784
2397	UUACCGUCAGUGUAUACGU	134	2397	UUACCGUCAGUGUAUACGU	134	2415	ACGUAUACACUGACGGUAA	1785
2415	UGGCAAGGAGCAGCUGCAA	135	2415	UGGCAAGGAGCAGCUGCAA	135	2433	UUGCAGCUGCUCCUUGCCA	1786
2433	ACUACUCAUGCCUCUUAAG	136	2433	ACUACUCAUGCCUCUUAAG	136	2451	CUUAAGAGGCAUGAGUAGU	1787
2451	GGCACCAAAAGAAGUAACC	137	2451	GGCACCAAAAGAAGUAACC	137	2469	GGUUACUUCUUUUGGUGCC	1788
2469	CUUUCUUGAAGGUGAUUCA	138	2469	CUUUCUUGAAGGUGAUUCA	138	2487	UGAAUCACCUUCAAGAAAG	1789
2487	ACAUGACACAGUACUUACC	139	2487	ACAUGACACAGUACUUACC	139	2505	GGUAAGUACUGUGUCAUGU	1790
2505	CUCUGAGGAGGUUGUUCUC	140	2505	CUCUGAGGAGGUUGUUCUC	140	2523	GAGAACAACCUCCUCAGAG	1791
2523	CAAGAACGGUGAACUCGAA	141	2523	CAAGAACGGUGAACUCGAA	141	2541	UUCGAGUUCACCGUUCUUG	1792
2541	AGCACUCGAGACGCCCGUU	142	2541	AGCACUCGAGACGCCCGUU	142	2559	AACGGGCGUCUCGAGUGCU	1793
2559	UGAUAGCUUCACAAAUGGA	143	2559	UGAUAGCUUCACAAAUGGA	143	2577	UCCAUUUGUGAAGCUAUCA	1794
2577	AGCUAUCGUCGGCACACCA	144	2577	AGCUAUCGUCGGCACACCA	144	2595	UGGUGUGCCGACGAUAGCU	1795
2595	AGUCUGUGUAAAUGGCCUC	145	2595	AGUCUGUGUAAAUGGCCUC	145	2613	GAGGCCAUUUACACAGACU	1796
2613	CAUGCUCUUAGAGAUUAAG	146	2613	CAUGCUCUUAGAGAUUAAG	146	2631	CUUAAUCUCUAAGAGCAUG	1797
2631	GGACAAAGAACAAUACUGC	147	2631	GGACAAAGAACAAUACUGC	147	2649	GCAGUAUUGUUCUUUGUCC	1798
2649	CGCAUUGUCUCCUGGUUUA	148	2649	CGCAUUGUCUCCUGGUUUA	148	2667	UAAACCAGGAGACAAUGCG	1799
2667	ACUGGCUACAAACAAUGUC	149	2667	ACUGGCUACAAACAAUGUC	149	2685	GACAUUGUUUGUAGCCAGU	1800
2685	CUUUCGCUUAAAAGGGGGU	150	2685	CUUUCGCUUAAAAGGGGGU	150	2703	ACCCCCUUUUAAGCGAAAG	1801
2703	UGCACCAAUUAAAGGUGUA	151	2703	UGCACCAAUUAAAGGUGUA	151	2721	UACACCUUUAAUUGGUGCA	1802
2721	AACCUUUGGAGAAGAUACU	152	2721	AACCUUUGGAGAAGAUACU	152	2739	AGUAUCUUCUCCAAAGGUU	1803
2739	UGUUUGGGAAGUUCAAGGU	153	2739	UGUUUGGGAAGUUCAAGGU	153	2757	ACCUUGAACUUCCCAAACA	1804
2757	UUACAAGAAUGUGAGAAUC	154	2757	UUACAAGAAUGUGAGAAUC	154	2775	GAUUCUCACAUUCUUGUAA	1805
2775	CACAUUUGAGCUUGAUGAA	155	2775	CACAUUUGAGCUUGAUGAA	155	2793	UUCAUCAAGCUCAAAUGUG	1806
2793	ACGUGUUGACAAAGUGCUU	156	2793	ACGUGUUGACAAAGUGCUU	156	2811	AAGCACUUUGUCAACACGU	1807
2811	UAAUGAAAAGUGCUCUGUC	157	2811	UAAUGAAAAGUGCUCUGUC	157	2829	GACAGAGCACUUUUCAUUA	1808
2829	CUACACUGUUGAAUCCGGU	158	2829	CUACACUGUUGAAUCCGGU	158	2847	ACCGGAUUCAACAGUGUAG	1809
2847	UACCGAAGUUACUGAGUUU	159	2847	UACCGAAGUUACUGAGUUU	159	2865	AAACUCAGUAACUUCGGUA	1810
2865	UGCAUGUGUUGUAGCAGAG	160	2865	UGCAUGUGUUGUAGCAGAG	160	2883	CUCUGCUACAACACAUGCA	1811
2883	GGCUGUUGUGAAGACUUUA	161	2883	GGCUGUUGUGAAGACUUUA	161	2901	UAAAGUCUUCACAACAGCC	1812
2901	ACAACCAGUUUCUGAUCUC	162	2901	ACAACCAGUUUCUGAUCUC	162	2919	GAGAUCAGAAACUGGUUGU	1813

2919	CCUUACCAACAUGGGUAUU	163	2919	CCUUACCAACAUGGGUAUU	163	2937	AAUACCCAUGUUGGUAAGG	1814
2937	UGAUCUUGAUGAGUGGAGU	164	2937	UGAUCUUGAUGAGUGGAGU	164	2955	ACUCCACUCAUCAAGAUCA	1815
2955	UGUAGCUACAUUCUACUUA	165	2955	UGUAGCUACAUUCUACUUA	165	2973	UAAGUAGAAUGUAGCUACA	1816
2973	AUUUGAUGAUGCUGGUGAA	166	2973	AUUUGAUGAUGCUGGUGAA	166	2991	UUCACCAGCAUCAUCAAAU	1817
2991	AGAAAACUUUUCAUCACGU	167	2991	AGAAAACUUUUCAUCACGU	167	3009	ACGUGAUGAAAAGUUUUCU	1818
3009	UAUGUAUUGUUCCUUUUAC	168	3009	UAUGUAUUGUUCCUUUUAC	168	3027	GUAAAAGGAACAAUACAUA	1819
3027	CCCUCCAGAUGAGGAAGAA	169	3027	CCCUCCAGAUGAGGAAGAA	169	3045	UUCUUCCUCAUCUGGAGGG	1820
3045	AGAGGACGAUGCAGAGUGU	170	3045	AGAGGACGAUGCAGAGUGU	170	3063	ACACUCUGCAUCGUCCUCU	1821
3063	UGAGGAAGAAGAAAUUGAU	171	3063	UGAGGAAGAAGAAAUUGAU	171	3081	AUCAAUUUCUUCUUCCUCA	1822
3081	UGAAACCUGUGAACAUGAG	172	3081	UGAAACCUGUGAACAUGAG	172	3099	CUCAUGUUCACAGGUUUCA	1823
3099	GUACGGUACAGAGGAUGAU	173	3099	GUACGGUACAGAGGAUGAU	173	3117	AUCAUCCUCUGUACCGUAC	1824
3117	UUAUCAAGGUCUCCCUCUG	174	3117	UUAUCAAGGUCUCCCUCUG	174	3135	CAGAGGGAGACCUUGAUAA	1825
3135	GGAAUUUGGUGCCUCAGCU	175	3135	GGAAUUUGGUGCCUCAGCU	175	3153	AGCUGAGGCACCAAAUUCC	1826
3153	UGAAACAGUUCGAGUUGAG	176	3153	UGAAACAGUUCGAGUUGAG	176	3171	CUCAACUCGAACUGUUUCA	1827
3171	GGAAGAAGAAGAGGAAGAC	177	3171	GGAAGAAGAAGAGGAAGAC	177	3189	GUCUUCCUCUUCUUCUUCC	1828
3189	CUGGCUGGAUGAUACUACU	178	3189	CUGGCUGGAUGAUACUACU	178	3207	AGUAGUAUCAUCCAGCCAG	1829
3207	UGAGCAAUCAGAGAUUGAG	179	3207	UGAGCAAUCAGAGAUUGAG	179	3225	CUCAAUCUCUGAUUGCUCA	1830
3225	GCCAGAACCAGAACCUACA	180	3225	GCCAGAACCAGAACCUACA	180	3243	UGUAGGUUCUGGUUCUGGC	1831
3243	ACCUGAAGAACCAGUUAAU	181	3243	ACCUGAAGAACCAGUUAAU	181	3261	AUUAACUGGUUCUUCAGGU	1832
3261	UCAGUUUACUGGUUAUUUA	182	3261	UCAGUUUACUGGUUAUUUA	182	3279	UAAAUAACCAGUAAACUGA	1833
3279	AAAACUUACUGACAAUGUU	183	3279	AAAACUUACUGACAAUGUU	183	3297	AACAUUGUCAGUAAGUUUU	1834
3297	UGCCAUUAAAUGUGUUGAC	184	3297	UGCCAUUAAAUGUGUUGAC	184	3315	GUCAACACAUUUAAUGGCA	1835
3315	CAUCGUUAAGGAGGCACAA	185	3315	CAUCGUUAAGGAGGCACAA	185	3333	UUGUGCCUCCUUAACGAUG	1836
3333	AAGUGCUAAUCCUAUGGUG	186	3333	AAGUGCUAAUCCUAUGGUG	186	3351	CACCAUAGGAUUAGCACUU	1837
3351	GAUUGUAAAUGCUGCUAAC	187	3351	GAUUGUAAAUGCUGCUAAC	187	3369	GUUAGCAGCAUUUACAAUC	1838
3369	CAUACACCUGAAACAUGGU	188	3369	CAUACACCUGAAACAUGGU	188	3387	ACCAUGUUUCAGGUGUAUG	1839
3387	UGGUGGUGUAGCAGGUGCA	189	3387	UGGUGGUGUAGCAGGUGCA	189	3405	UGCACCUGCUACACCACCA	1840
3405	ACUCAACAAGGCAACCAAU	190	3405	ACUCAACAAGGCAACCAAU	190	3423	AUUGGUUGCCUUGUUGAGU	1841
3423	UGGUGCCAUGCAAAAGGAG	191	3423	UGGUGCCAUGCAAAAGGAG	191	3441	CUCCUUUUGCAUGGCACCA	1842
3441	GAGUGAUGAUUACAUUAAG	192	3441	GAGUGAUGAUUACAUUAAG	192	3459	CUUAAUGUAAUCAUCACUC	1843
3459	GCUAAAUGGCCCUCUUACA	193	3459	GCUAAAUGGCCCUCUUACA	193	3477	UGUAAGAGGGCCAUUUAGC	1844
3477	AGUAGGAGGGUCUUGUUUG	194	3477	AGUAGGAGGGUCUUGUUUG	194	3495	CAAACAAGACCCUCCUACU	1845
3495	GCUUUCUGGACAUAAUCUU	195	3495	GCUUUCUGGACAUAAUCUU	195	3513	AAGAUUAUGUCCAGAAAGC	1846
3513	UGCUAAGAAGUGUCUGCAU	196	3513	UGCUAAGAAGUGUCUGCAU	196	3531	AUGCAGACACUUCUUAGCA	1847
3531	UGUUGUUGGACCUAACCUA	197	3531	UGUUGUUGGACCUAACCUA	197	3549	UAGGUUAGGUCCAACAACA	1848
3549	AAAUGCAGGUGAGGACAUC	198	3549	AAAUGCAGGUGAGGACAUC	198	3567	GAUGUCCUCACCUGCAUUU	1849
3567	CCAGCUUCUUAAGGCAGCA	199	3567	CCAGCUUCUUAAGGCAGCA	199	3585	UGCUGCCUUAAGAAGCUGG	1850
3585	AUAUGAAAAUUUCAAUUCA	200	3585	AUAUGAAAAUUUCAAUUCA	200	3603	UGAAUUGAAAUUUUCAUAU	1851
3603	ACAGGACAUCUUACUUGCA	201	3603	ACAGGACAUCUUACUUGCA	201	3621	UGCAAGUAAGAUGUCCUGU	1852
3621	ACCAUUGUUGUCAGCAGGC	202	3621	ACCAUUGUUGUCAGCAGGC	202	3639	GCCUGCUGACAACAAUGGU	1853
3639	CAUAUUUGGUGCUAAACCA	203	3639	CAUAUUUGGUGCUAAACCA	203	3657	UGGUUUAGCACCAAAUAUG	1854
3657	ACUUCAGUCUUUACAAGUG	204	3657	ACUUCAGUCUUUACAAGUG	204	3675	CACUUGUAAAGACUGAAGU	1855

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3675	GUGCGUGCAGACGGUUCGU	205	3675	GUGCGUGCAGACGGUUCGU	205	3693	ACGAACCGUCUGCACGCAC	1856
3693	UACACAGGUUUAUAUUGCA	206	3693	UACACAGGUUUAUAUUGCA	206	3711	UGCAAUAUAAACCUGUGUA	1857
3711	AGUCAAUGACAAAGCUCUU	207	3711	AGUCAAUGACAAAGCUCUU	207	3729	AAGAGCUUUGUCAUUGACU	1858
3729	UUAUGAGCAGGUUGUCAUG	208	3729	UUAUGAGCAGGUUGUCAUG	208	3747	CAUGACAACCUGCUCAUAA	1859
3747	GGAUUAUCUUGAUAACCUG	209	3747	GGAUUAUCUUGAUAACCUG	209	3765	CAGGUUAUCAAGAUAAUCC	1860
3765	GAAGCCUAGAGUGGAAGCA	210	3765	GAAGCCUAGAGUGGAAGCA	210	3783	UGCUUCCACUCUAGGCUUC	1861
3783	ACCUAAACAAGAGGAGCCA	211	3783	ACCUAAACAAGAGGAGCCA	211	3801	UGGCUCCUCUUGUUUAGGU	1862
3801	ACCAAACACAGAAGAUUCC	212	3801	ACCAAACACAGAAGAUUCC	212	3819	GGAAUCUUCUGUGUUUGGU	1863
3819	CAAAACUGAGGAGAAAUCU	213	3819	CAAAACUGAGGAGAAAUCU	213	3837	AGAUUUCUCCUCAGUUUUG	1864
3837	UGUCGUACAGAAGCCUGUC	214	3837	UGUCGUACAGAAGCCUGUC	214	3855	GACAGGCUUCUGUACGACA	1865
3855	CGAUGUGAAGCCAAAAAUU	215	3855	CGAUGUGAAGCCAAAAAUU	215	3873	AAUUUUUGGCUUCACAUCG	1866
3873	UAAGGCCUGCAUUGAUGAG	216	3873	UAAGGCCUGCAUUGAUGAG	216	3891	CUCAUCAAUGCAGGCCUUA	1867
3891	GGUUACCACAACACUGGAA	217	3891	GGUUACCACAACACUGGAA	217	3909	UUCCAGUGUUGUGGUAACC	1868
3909	AGAAACUAAGUUUCUUACC	218	3909	AGAAACUAAGUUUCUUACC	218	3927	GGUAAGAAACUUAGUUUCU	1869
3927	CAAUAAGUUACUCUUGUUU	219	3927	CAAUAAGUUACUCUUGUUU	219	3945	AAACAAGAGUAACUUAUUG	1870
3945	UGCUGAUAUCAAUGGUAAG	220	3945	UGCUGAUAUCAAUGGUAAG	220	3963	CUUACCAUUGAUAUCAGCA	1871
3963	GCUUUACCAUGAUUCUCAG	221	3963	GCUUUACCAUGAUUCUCAG	221	3981	CUGAGAAUCAUGGUAAAGC	1872
3981	GAACAUGCUUAGAGGUGAA	222	3981	GAACAUGCUUAGAGGUGAA	222	3999	UUCACCUCUAAGCAUGUUC	1873
3999	AGAUAUGUCUUUCCUUGAG	223	3999	AGAUAUGUCUUUCCUUGAG	223	4017	CUCAAGGAAAGACAUAUCU	1874
4017	GAAGGAUGCACCUUACAUG	224	4017	GAAGGAUGCACCUUACAUG	224	4035	CAUGUAAGGUGCAUCCUUC	1875
4035	GGUAGGUGAUGUUAUCACU	225	4035	GGUAGGUGAUGUUAUCACU	225	4053	AGUGAUAACAUCACCUACC	1876
4053	UAGUGGUGAUAUCACUUGU	226	4053	UAGUGGUGAUAUCACUUGU	226	4071	ACAAGUGAUAUCACCACUA	1877
4071	UGUUGUAAUACCCUCCAAA	227	4071	UGUUGUAAUACCCUCCAAA	227	4089	UUUGGAGGGUAUUACAACA	1878
4089	AAAGGCUGGUGGCACUACU	228	4089	AAAGGCUGGUGGCACUACU	228	4107	AGUAGUGCCACCAGCCUUU	1879
4107	UGAGAUGCUCUCAAGAGCU	229	4107	UGAGAUGCUCUCAAGAGCU	229	4125	AGCUCUUGAGAGCAUCUCA	1880
4125	UUUGAAGAAAGUGCCAGUU	230	4125	UUUGAAGAAAGUGCCAGUU	230	4143	AACUGGCACUUUCUUCAAA	1881
4143	UGAUGAGUAUAUAACCACG	231	4143	UGAUGAGUAUAUAACCACG	231	4161	CGUGGUUAUAUACUCAUCA	1882
4161	GUACCCUGGACAAGGAUGU	232	4161	GUACCCUGGACAAGGAUGU	232	4179	ACAUCCUUGUCCAGGGUAC	1883
4179	UGCUGGUUAUACACUUGAG	233	4179	UGCUGGUUAUACACUUGAG	233	4197	CUCAAGUGUAUAACCAGCA	1884
4197	GGAAGCUAAGACUGCUCUU	234	4197	GGAAGCUAAGACUGCUCUU	234	4215	AAGAGCAGUCUUAGCUUCC	1885
4215	UAAGAAAUGCAAAUCUGCA	235	4215	UAAGAAAUGCAAAUCUGCA	235	4233	UGCAGAUUUGCAUUUCUUA	1886
4233	AUUUUAUGUACUACCUUCA	236	4233	AUUUUAUGUACUACCUUCA	236	4251	UGAAGGUAGUACAUAAAAU	1887
4251	AGAAGCACCUAAUGCUAAG	237	4251	AGAAGCACCUAAUGCUAAG	237	4269	CUUAGCAUUAGGUGCUUCU	1888
4269	GGAAGAGAUUCUAGGAACU	238	4269	GGAAGAGAUUCUAGGAACU	238	4287	AGUUCCUAGAAUCUCUUCC	1889
4287	UGUAUCCUGGAAUUUGAGA	239	4287	UGUAUCCUGGAAUUUGAGA	239	4305	UCUCAAAUUCCAGGAUACA	1890
4305	AGAAAUGCUUGCUCAUGCU	240	4305	AGAAAUGCUUGCUCAUGCU	240	4323	AGCAUGAGCAAGCAUUUCU	1891
4323	UGAAGAGACAAGAAAAUUA	241	4323	UGAAGAGACAAGAAAAUUA	241	4341	UAAUUUUCUUGUCUCUUCA	1892
4341	AAUGCCUAUAUGCAUGGAU	242	4341	AAUGCCUAUAUGCAUGGAU	242	4359	AUCCAUGCAUAUAGGCAUU	1893
4359	UGUUAGAGCCAUAAUGGCA	243	4359	UGUUAGAGCCAUAAUGGCA	243	4377	UGCCAUUAUGGCUCUAACA	1894
4377	AACCAUCCAACGUAAGUAU	244	4377	AACCAUCCAACGUAAGUAU	244	4395	AUACUUACGUUGGAUGGUU	1895
4395	UAAAGGAAUUAAAAUUCAA	245	4395	UAAAGGAAUUAAAAUUCAA	245	4413	UUGAAUUUUAAUUCCUUUA	1896
4413	AGAGGGCAUCGUUGACUAU	246	4413	AGAGGGCAUCGUUGACUAU	246	4431	AUAGUCAACGAUGCCCUCU	1897

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4431	UGGUGUCCGAUUCUUCUUU	247	4431	UGGUGUCCGAUUCUUCUUU	247	4449	AAAGAAGAAUCGGACACCA	1898
4449	UUAUACUAGUAAAGAGCCU	248	4449	UUAUACUAGUAAAGAGCCU	248	4467	AGGCUCUUUACUAGUAUAA	1899
4467	UGUAGCUUCUAUUAUUACG	249	4467	UGUAGCUUCUAUUAUUACG	249	4485	CGUAAUAAUAGAAGCUACA	1900
4485	GAAGCUGAACUCUCUAAAU	250	4485	GAAGCUGAACUCUCUAAAU	250	4503	AUUUAGAGAGUUCAGCUUC	1901
4503	UGAGCCGCUUGUCACAAUG	251	4503	UGAGCCGCUUGUCACAAUG	251	4521	CAUUGUGACAAGCGGCUCA	1902
4521	GCCAAUUGGUUAUGUGACA	252	4521	GCCAAUUGGUUAUGUGACA	252	4539	UGUCACAUAACCAAUUGGC	1903
4539	ACAUGGUUUUAAUCUUGAA	253	4539	ACAUGGUUUUAAUCUUGAA	253	4557	UUCAAGAUUAAAACCAUGU	1904
4557	AGAGGCUGCGCGCUGUAUG	254	4557	AGAGGCUGCGCGCUGUAUG	254	4575	CAUACAGCGCGCAGCCUCU	1905
4575	GCGUUCUCUUAAAGCUCCU	255	4575	GCGUUCUCUUAAAGCUCCU	255	4593	AGGAGCUUUAAGAGAACGC	1906
4593	UGCCGUAGUGUCAGUAUCA	256	4593	UGCCGUAGUGUCAGUAUCA	256	4611	UGAUACUGACACUACGGCA	1907
4611	AUCACCAGAUGCUGUUACU	257	4611	AUCACCAGAUGCUGUUACU	257	4629	AGUAACAGCAUCUGGUGAU	1908
4629	UACAUAUAAUGGAUACCUC	258	4629	UACAUAUAAUGGAUACCUC	258	4647	GAGGUAUCCAUUAUAUGUA	1909
4647	CACUUCGUCAUCAAAGACA	259	4647	CACUUCGUCAUCAAAGACA	259	4665	UGUCUUUGAUGACGAAGUG	1910
4665	AUCUGAGGAGCACUUUGUA	260	4665	AUCUGAGGAGCACUUUGUA	260	4683	UACAAAGUGCUCCUCAGAU	1911
4683	AGAAACAGUUUCUUUGGCU	261	4683	AGAAACAGUUUCUUUGGCU	261	4701	AGCCAAAGAAACUGUUUCU	1912
4701	UGGCUCUUACAGAGAUUGG	262	4701	UGGCUCUUACAGAGAUUGG	262	4719	CCAAUCUCUGUAAGAGCCA	1913
4719	GUCCUAUUCAGGACAGCGU	263	4719	GUCCUAUUCAGGACAGCGU	263	4737	ACGCUGUCCUGAAUAGGAC	1914
4737	UACAGAGUUAGGUGUUGAA	264	4737	UACAGAGUUAGGUGUUGAA	264	4755	UUCAACACCUAACUCUGUA	1915
4755	AUUUCUUAAGCGUGGUGAC	265	4755	AUUUCUUAAGCGUGGUGAC	265	4773	GUCACCACGCUUAAGAAAU	1916
4773	CAAAAUUGUGUACCACACU	266	4773	CAAAAUUGUGUACCACACU	266	4791	AGUGUGGUACACAAUUUUG	1917
4791	UCUGGAGAGCCCCGUCGAG	267	4791	UCUGGAGAGCCCCGUCGAG	267	4809	CUCGACGGGGCUCUCCAGA	1918
4809	GUUUCAUCUUGACGGUGAG	268	4809	GUUUCAUCUUGACGGUGAG	268	4827	CUCACCGUCAAGAUGAAAC	1919
4827	GGUUCUUUCACUUGACAAA	269	4827	GGUUCUUUCACUUGACAAA	269	4845	UUUGUCAAGUGAAAGAACC	1920
4845	ACUAAAGAGUCUCUUAUCC	270	4845	ACUAAAGAGUCUCUUAUCC	270	4863	GGAUAAGAGACUCUUUAGU	1921
4863	CCUGCGGGAGGUUAAGACU	271	4863	CCUGCGGGAGGUUAAGACU	271	4881	AGUCUUAACCUCCCGCAGG	1922
4881	UAUAAAAGUGUUCACAACU	272	4881	UAUAAAAGUGUUCACAACU	272	4899	AGUUGUGAACACUUUUAUA	1923
4899	UGUGGACAACACUAAUCUC	273	4899	UGUGGACAACACUAAUCUC	273	4917	GAGAUUAGUGUUGUCCACA	1924
4917	CCACACACAGCUUGUGGAU	274	4917	CCACACACAGCUUGUGGAU	274	4935	AUCCACAAGCUGUGUGUGG	1925
4935	UAUGUCUAUGACAUAUGGA	275	4935	UAUGUCUAUGACAUAUGGA	275	4953	UCCAUAUGUCAUAGACAUA	1926
4953	ACAGCAGUUUGGUCCAACA	276	4953	ACAGCAGUUUGGUCCAACA	276	4971	UGUUGGACCAAACUGCUGU	1927
4971	AUACUUGGAUGGUGCUGAU	277	4971	AUACUUGGAUGGUGCUGAU	277	4989	AUCAGCACCAUCCAAGUAU	1928
4989	UGUUACAAAAAUUAAACCU	278	4989	UGUUACAAAAAUUAAACCU	278	5007	AGGUUUAAUUUUUGUAACA	1929
5007	UCAUGUAAAUCAUGAGGGU	279	5007	UCAUGUAAAUCAUGAGGGU	279	5025	ACCCUCAUGAUUUACAUGA	1930
5025	UAAGACUUUCUUUGUACUA	280	5025	UAAGACUUUCUUUGUACUA	280	5043	UAGUACAAAGAAAGUCUUA	1931
5043	ACCUAGUGAUGACACACUA	281	5043	ACCUAGUGAUGACACACUA	281	5061	UAGUGUGUCAUCACUAGGU	1932
5061	ACGUAGUGAAGCUUUCGAG	282	5061	ACGUAGUGAAGCUUUCGAG	282	5079	CUCGAAAGCUUCACUACGU	1933
5079	GUACUACCAUACUCUUGAU	283	5079	GUACUACCAUACUCUUGAU	283	5097	AUCAAGAGUAUGGUAGUAC	1934
5097	UGAGAGUUUUCUUGGUAGG	284	5097	UGAGAGUUUUCUUGGUAGG	284	5115	CCUACCAAGAAAACUCUCA	1935
5115	GUACAUGUCUGCUUUAAAC	285	5115	GUACAUGUCUGCUUUAAAC	285	5133	GUUUAAAGCAGACAUGUAC	1936
5133	CCACACAAAGAAAUGGAAA	286	5133	CCACACAAAGAAAUGGAAA	286	5151	UUUCCAUUUCUUUGUGUGG	1937
5151	AUUUCCUCAAGUUGGUGGU	287	5151	AUUUCCUCAAGUUGGUGGU	287	5169	ACCACCAACUUGAGGAAAU	1938
5169	UUUAACUUCAAUUAAAUGG	288	5169	UUUAACUUCAAUUAAAUGG	288	5187	CCAUUUAAUUGAAGUUAAA	1939

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5187	GGCUGAUAACAAUUGUUAU	289	5187	GGCUGAUAACAAUUGUUAU	289	5205	AUAACAAUUGUUAUCAGCC	1940
5205	UUUGUCUAGUGUUUUAUUA	290	5205	UUUGUCUAGUGUUUUAUUA	290	5223	UAAUAAAACACUAGACAAA	1941
5223	AGCACUUCAACAGCUUGAA	291	5223	AGCACUUCAACAGCUUGAA	291	5241	UUCAAGCUGUUGAAGUGCU	1942
5241	AGUCAAAUUCAAUGCACCA	292	5241	AGUCAAAUUCAAUGCACCA	292	5259	UGGUGCAUUGAAUUUGACU	1943
5259	AGCACUUCAAGAGGCUUAU	293	5259	AGCACUUCAAGAGGCUUAU	293	5277	AUAAGCCUCUUGAAGUGCU	1944
5277	UUAUAGAGCCCGUGCUGGU	294	5277	UUAUAGAGCCCGUGCUGGU	294	5295	ACCAGCACGGGCUCUAUAA	1945
5295	UGAUGCUGCUAACUUUUGU	295	5295	UGAUGCUGCUAACUUUUGU	295	5313	ACAAAAGUUAGCAGCAUCA	1946
5313	UGCACUCAUACUCGCUUAC	296	5313	UGCACUCAUACUCGCUUAC	296	5331	GUAAGCGAGUAUGAGUGCA	1947
5331	CAGUAAUAAAACUGUUGGC	297	5331	CAGUAAUAAAACUGUUGGC	297	5349	GCCAACAGUUUUAUUACUG	1948
5349	CGAGCUUGGUGAUGUCAGA	298	5349	CGAGCUUGGUGAUGUCAGA	298	5367	UCUGACAUCACCAAGCUCG	1949
5367	AGAAACUAUGACCCAUCUU	299	5367	AGAAACUAUGACCCAUCUU	299	5385	AAGAUGGGUCAUAGUUUCU	1950
5385	UCUACAGCAUGCUAAUUUG	300	5385	UCUACAGCAUGCUAAUUUG	300	5403	CAAAUUAGCAUGCUGUAGA	1951
5403	GGAAUCUGCAAAGCGAGUU	301	5403	GGAAUCUGCAAAGCGAGUU	301	5421	AACUCGCUUUGCAGAUUCC	1952
5421	UCUUAAUGUGGUGUGUAAA	302	5421	UCUUAAUGUGGUGUGUAAA	302	5439	UUUACACACCACAUUAAGA	1953
5439	ACAUUGUGGUCAGAAAACU	303	5439	ACAUUGUGGUCAGAAAACU	303	5457	AGUUUUCUGACCACAAUGU	1954
5457	UACUACCUUAACGGGUGUA	304	5457	UACUACCUUAACGGGUGUA	304	5475	UACACCCGUUAAGGUAGUA	1955
5475	AGAAGCUGUGAUGUAUAUG	305	5475	AGAAGCUGUGAUGUAUAUG	305	5493	CAUAUACAUCACAGCUUCU	1956
5493	GGGUACUCUAUCUUAUGAU	306	5493	GGGUACUCUAUCUUAUGAU	306	5511	AUCAUAAGAUAGAGUACCC	1957
5511	UAAUCUUAAGACAGGUGUU	307	5511	UAAUCUUAAGACAGGUGUU	307	5529	AACACCUGUCUUAAGAUUA	1958
5529	UUCCAUUCCAUGUGUGUGU	308	5529	UUCCAUUCCAUGUGUGUGU	308	5547	ACACACACAUGGAAUGGAA	1959
5547	UGGUCGUGAUGCUACACAA	309	5547	UGGUCGUGAUGCUACACAA	309	5565	UUGUGUAGCAUCACGACCA	1960
5565	AUAUCUAGUACAACAAGAG	310	5565	AUAUCUAGUACAACAAGAG	310	5583	CUCUUGUUGUACUAGAUAU	1961
5583	GUCUUCUUUUGUUAUGAUG	311	5583	GUCUUCUUUUGUUAUGAUG	311	5601	CAUCAUAACAAAAGAAGAC	1962
5601	GUCUGCACCACCUGCUGAG	312	5601	GUCUGCACCACCUGCUGAG	312	5619	CUCAGCAGGUGGUGCAGAC	1963
5619	GUAUAAAUUACAGCAAGGU	313	5619	GUAUAAAUUACAGCAAGGU	313	5637	ACCUUGCUGUAAUUUAUAC	1964
5637	UACAUUCUUAUGUGCGAAU	314	5637	UACAUUCUUAUGUGCGAAU	314	5655	AUUCGCACAUAAGAAUGUA	1965
5655	UGAGUACACUGGUAACUAU	315	5655	UGAGUACACUGGUAACUAU	315	5673	AUAGUUACCAGUGUACUCA	1966
5673	UCAGUGUGGUCAUUACACU	316	5673	UCAGUGUGGUCAUUACACU	316	5691	AGUGUAAUGACCACACUGA	1967
5691	UCAUAUAACUGCUAAGGAG	317	5691	UCAUAUAACUGCUAAGGAG	317	5709	CUCCUUAGCAGUUAUAUGA	1968
5709	GACCCUCUAUCGUAUUGAC	318	5709	GACCCUCUAUCGUAUUGAC	318	5727	GUCAAUACGAUAGAGGGUC	1969
5727	CGGAGCUCACCUUACAAAG	319	5727	CGGAGCUCACCUUACAAAG	319	5745	CUUUGUAAGGUGAGCUCCG	1970
5745	GAUGUCAGAGUACAAAGGA	320	5745	GAUGUCAGAGUACAAAGGA	320	5763	UCCUUUGUACUCUGACAUC	1971
5763	ACCAGUGACUGAUGUUUUC	321	5763	ACCAGUGACUGAUGUUUUC	321	5781	GAAAACAUCAGUCACUGGU	1972
5781	CUACAAGGAAACAUCUUAC	322	5781	CUACAAGGAAACAUCUUAC	322	5799	GUAAGAUGUUUCCUUGUAG	1973
5799	CACUACAACCAUCAAGCCU	323	5799	CACUACAACCAUCAAGCCU	323	5817	AGGCUUGAUGGUUGUAGUG	1974
5817	UGUGUCGUAUAAACUCGAU	324	5817	UGUGUCGUAUAAACUCGAU	324	5835	AUCGAGUUUAUACGACACA	1975
5835	UGGAGUUACUUACACAGAG	325	5835	UGGAGUUACUUACACAGAG	325	5853	CUCUGUGUAAGUAACUCCA	1976
5853	GAUUGAACCAAAAUUGGAU	326	5853	GAUUGAACCAAAAUUGGAU	326	5871	AUCCAAUUUUGGUUCAAUC	1977
5871	UGGGUAUUAUAAAAAGGAU	327	5871	UGGGUAUUAUAAAAAGGAU	327	5889	AUCCUUUUUAUAAUACCCA	1978
5889	UAAUGCUUACUAUACAGAG	328	5889	UAAUGCUUACUAUACAGAG	328	5907	CUCUGUAUAGUAAGCAUUA	1979
5907	GCAGCCUAUAGACCUUGUA	329	5907	GCAGCCUAUAGACCUUGUA	329	5925	UACAAGGUCUAUAGGCUGC	1980
5925	ACCAACUCAACCAUUACCA	330	5925	ACCAACUCAACCAUUACCA	330	5943	UGGUAAUGGUUGAGUUGGU	1981

5943	AAAUGCGAGUUUUGAUAAU	331	5943	AAAUGCGAGUUUUGAUAAU	331	5961	AUUAUCAAAACUCGCAUUU	1982
5961	UUUCAAACUCACAUGUUCU	332	5961	UUUCAAACUCACAUGUUCU	332	5979	AGAACAUGUGAGUUUGAAA	1983
5979	UAACACAAAAUUUGCUGAU	333	5979	UAACACAAAAUUUGCUGAU	333	5997	AUCAGCAAAUUUUGUGUUA	1984
5997	UGAUUUAAAUCAAAUGACA	334	5997	UGAUUUAAAUCAAAUGACA	334	6015	UGUCAUUUGAUUUAAAUCA	1985
6015	AGGCUUCACAAAGCCAGCU	335	6015	AGGCUUCACAAAGCCAGCU	335	6033	AGCUGGCUUUGUGAAGCCU	1986
6033	UUCACGAGAGCUAUCUGUC	336	6033	UUCACGAGAGCUAUCUGUC	336	6051	GACAGAUAGCUCUCGUGAA	1987
6051	CACAUUCUUCCCAGACUUG	337	6051	CACAUUCUUCCCAGACUUG	337	6069	CAAGUCUGGGAAGAAUGUG	1988
6069	GAAUGGCGAUGUAGUGGCU	338	6069	GAAUGGCGAUGUAGUGGCU	338	6087	AGCCACUACAUCGCCAUUC	1989
6087	UAUUGACUAUAGACACUAU	339	6087	UAUUGACUAUAGACACUAU	339	6105	AUAGUGUCUAUAGUCAAUA	1990
6105	UUCAGCGAGUUUCAAGAAA	340	6105	UUCAGCGAGUUUCAAGAAA	340	6123	UUUCUUGAAACUCGCUGAA	1991
6123	AGGUGCUAAAUUACUGCAU	341	6123	AGGUGCUAAAUUACUGCAU	341	6141	AUGCAGUAAUUUAGCACCU	1992
6141	UAAGCCAAUUGUUUGGCAC	342	6141	UAAGCCAAUUGUUUGGCAC	342	6159	GUGCCAAACAAUUGGCUUA	1993
6159	CAUUAACCAGGCUACAACC	343	6159	CAUUAACCAGGCUACAACC	343	6177	GGUUGUAGCCUGGUUAAUG	1994
6177	CAAGACAACGUUCAAACCA	344	6177	CAAGACAACGUUCAAACCA	344	6195	UGGUUUGAACGUUGUCUUG	1995
6195	AAACACUUGGUGUUUACGU	345	6195	AAACACUUGGUGUUUACGU	345	6213	ACGUAAACACCAAGUGUUU	1996
6213	UUGUCUUUGGAGUACAAAG	346	6213	UUGUCUUUGGAGUACAAAG	346	6231	CUUUGUACUCCAAAGACAA	1997
6231	GCCAGUAGAUACUUCAAAU	347	6231	GCCAGUAGAUACUUCAAAU	347	6249	AUUUGAAGUAUCUACUGGC	1998
6249	UUCAUUUGAAGUUCUGGCA	348	6249	UUCAUUUGAAGUUCUGGCA	348	6267	UGCCAGAACUUCAAAUGAA	1999
6267	AGUAGAAGACACACAAGGA	349	6267	AGUAGAAGACACACAAGGA	349	6285	UCCUUGUGUGUCUUCUACU	2000
6285	AAUGGACAAUCUUGCUUGU	350	6285	AAUGGACAAUCUUGCUUGU	350	6303	ACAAGCAAGAUUGUCCAUU	2001
6303	UGAAAGUCAACAACCCACC	351	6303	UGAAAGUCAACAACCCACC	351	6321	GGUGGGUUGUUGACUUUCA	2002
6321	CUCUGAAGAAGUAGUGGAA	352	6321	CUCUGAAGAAGUAGUGGAA	352	6339	UUCCACUACUUCUUCAGAG	2003
6339	AAAUCCUACCAUACAGAAG	353	6339	AAAUCCUACCAUACAGAAG	353	6357	CUUCUGUAUGGUAGGAUUU	2004
6357	GGAAGUCAUAGAGUGUGAC	354	6357	GGAAGUCAUAGAGUGUGAC	354	6375	GUCACACUCUAUGACUUCC	2005
6375	CGUGAAAACUACCGAAGUU	355	6375	CGUGAAAACUACCGAAGUU	355	6393	AACUUCGGUAGUUUUCACG	2006
6393	UGUAGGCAAUGUCAUACUU	356	6393	UGUAGGCAAUGUCAUACUU	356	6411	AAGUAUGACAUUGCCUACA	2007
6411	UAAACCAUCAGAUGAAGGU	357	6411	UAAACCAUCAGAUGAAGGU	357	6429	ACCUUCAUCUGAUGGUUUA	2008
6429	UGUUAAAGUAACACAAGAG	358	6429	UGUUAAAGUAACACAAGAG	358	6447	CUCUUGUGUUACUUUAACA	2009
6447	GUUAGGUCAUGAGGAUCUU	359	6447	GUUAGGUCAUGAGGAUCUU	359	6465	AAGAUCCUCAUGACCUAAC	2010
6465	UAUGGCUGCUUAUGUGGAA	360	6465	UAUGGCUGCUUAUGUGGAA	360	6483	UUCCACAUAAGCAGCCAUA	2011
6483	AAACACAAGCAUUACCAUU	361	6483	AAACACAAGCAUUACCAUU	361	6501	AAUGGUAAUGCUUGUGUUU	2012
6501	UAAGAAACCUAAUGAGCUU	362	6501	UAAGAAACCUAAUGAGCUU	362	6519	AAGCUCAUUAGGUUUCUUA	2013
6519	UUCACUAGCCUUAGGUUUA	363	6519	UUCACUAGCCUUAGGUUUA	363	6537	UAAACCUAAGGCUAGUGAA	2014
6537	AAAAACAAUUGCCACUCAU	364	6537	AAAAACAAUUGCCACUCAU	364	6555	AUGAGUGGCAAUUGUUUUU	2015
6555	UGGUAUUGCUGCAAUUAAU	365	6555	UGGUAUUGCUGCAAUUAAU	365	6573	AUUAAUUGCAGCAAUACCA	2016
6573	UAGUGUUCCUUGGAGUAAA	366	6573	UAGUGUUCCUUGGAGUAAA	366	6591	UUUACUCCAAGGAACACUA	2017
6591	AAUUUUGGCUUAUGUCAAA	367	6591	AAUUUUGGCUUAUGUCAAA	367	6609	UUUGACAUAAGCCAAAAUU	2018
6609	ACCAUUCUUAGGACAAGCA	368	6609	ACCAUUCUUAGGACAAGCA	368	6627	UGCUUGUCCUAAGAAUGGU	2019
6627	AGCAAUUACAACAUCAAAU	369	6627	AGCAAUUACAACAUCAAAU	369	6645	AUUUGAUGUUGUAAUUGCU	2020
6645	UUGCGCUAAGAGAUUAGCA	370	6645	UUGCGCUAAGAGAUUAGCA	370	6663	UGCUAAUCUCUUAGCGCAA	2021
6663	ACAACGUGUGUUUAACAAU	371	6663	ACAACGUGUGUUUAACAAU	371	6681	AUUGUUAAACACACGUUGU	2022
6681	UUAUAUGCCUUAUGUGUUU	372	6681	UUAUAUGCCUUAUGUGUUU	372	6699	AAACACAUAAGGCAUAUAA	2023

6699	UACAUUAUUGUUCCAAUUG	373	6699	UACAUUAUUGUUCCAAUUG	373	6717	CAAUUGGAACAAUAAUGUA	2024
6717	GUGUACUUUUACUAAAAGU	374	6717	GUGUACUUUUACUAAAAGU	374	6735	ACUUUUAGUAAAAGUACAC	2025
6735	UACCAAUUCUAGAAUUAGA	375	6735	UACCAAUUCUAGAAUUAGA	375	6753	UCUAAUUCUAGAAUUGGUA	2026
6753	AGCUUCACUACCUACAACU	376	6753	AGCUUCACUACCUACAACU	376	6771	AGUUGUAGGUAGUGAAGCU	2027
6771	UAUUGCUAAAAAUAGUGUU	377	6771	UAUUGCUAAAAAUAGUGUU	377	6789	AACACUAUUUUUAGCAAUA	2028
6789	UAAGAGUGUUGCUAAAUUA	378	6789	UAAGAGUGUUGCUAAAUUA	378	6807	UAAUUUAGCAACACUCUUA	2029
6807	AUGUUUGGAUGCCGGCAUU	379	6807	AUGUUUGGAUGCCGGCAUU	379	6825	AAUGCCGGCAUCCAAACAU	2030
6825	UAAUUAUGUGAAGUCACCC	380	6825	UAAUUAUGUGAAGUCACCC	380	6843	GGGUGACUUCACAUAAUUA	2031
6843	CAAAUUUUCUAAAUUGUUC	381	6843	CAAAUUUUCUAAAUUGUUC	381	6861	GAACAAUUUAGAAAAUUUG	2032
6861	CACAAUCGCUAUGUGGCUA	382	6861	CACAAUCGCUAUGUGGCUA	382	6879	UAGCCACAUAGCGAUUGUG	2033
6879	AUUGUUGUUAAGUAUUUGC	383	6879	AUUGUUGUUAAGUAUUUGC	383	6897	GCAAAUACUUAACAACAAU	2034
6897	CUUAGGUUCUCUAAUCUGU	384	6897	CUUAGGUUCUCUAAUCUGU	384	6915	ACAGAUUAGAGAACCUAAG	2035
6915	UGUAACUGCUGCUUUUGGU	385	6915	UGUAACUGCUGCUUUUGGU	385	6933	ACCAAAAGCAGCAGUUACA	2036
6933	UGUACUCUUAUCUAAUUUU	386	6933	UGUACUCUUAUCUAAUUUU	386	6951	AAAAUUAGAUAAGAGUACA	2037
6951	UGGUGCUCCUUCUUAUUGU	387	6951	UGGUGCUCCUUCUUAUUGU	387	6969	ACAAUAAGAAGGAGCACCA	2038
6969	UAAUGGCGUUAGAGAAUUG	388	6969	UAAUGGCGUUAGAGAAUUG	388	6987	CAAUUCUCUAACGCCAUUA	2039
6987	GUAUCUUAAUUCGUCUAAC	389	6987	GUAUCUUAAUUCGUCUAAC	389	7005	GUUAGACGAAUUAAGAUAC	2040
7005	CGUUACUACUAUGGAUUUC	390	7005	CGUUACUACUAUGGAUUUC	390	7023	GAAAUCCAUAGUAGUAACG	2041
7023	CUGUGAAGGUUCUUUUCCU	391	7023	CUGUGAAGGUUCUUUUCCU	391	7041	AGGAAAAGAACCUUCACAG	2042
7041	UUGCAGCAUUUGUUUAAGU	392	7041	UUGCAGCAUUUGUUUAAGU	392	7059	ACUUAAACAAAUGCUGCAA	2043
7059	UGGAUUAGACUCCCUUGAU	393	7059	UGGAUUAGACUCCCUUGAU	393	7077	AUCAAGGGAGUCUAAUCCA	2044
7077	UUCUUAUCCAGCUCUUGAA	394	7077	UUCUUAUCCAGCUCUUGAA	394	7095	UUCAAGAGCUGGAUAAGAA	2045
7095	AACCAUUCAGGUGACGAUU	395	7095	AACCAUUCAGGUGACGAUU	395	7113	AAUCGUCACCUGAAUGGUU	2046
7113	UUCAUCGUACAAGCUAGAC	396	7113	UUCAUCGUACAAGCUAGAC	396	7131	GUCUAGCUUGUACGAUGAA	2047
7131	CUUGACAAUUUUAGGUCUG	397	7131	CUUGACAAUUUUAGGUCUG	397	7149	CAGACCUAAAAUUGUCAAG	2048
7149	GGCCGCUGAGUGGGUUUUG	398	7149	GGCCGCUGAGUGGGUUUUG	398	7167	CAAAACCCACUCAGCGGCC	2049
7167	GGCAUAUAUGUUGUUCACA	399	7167	GGCAUAUAUGUUGUUCACA	399	7185	UGUGAACAACAUAUAUGCC	2050
7185	AAAAUUCUUUUAUUUAUUA	400	7185	AAAAUUCUUUUAUUUAUUA	400	7203	UAAUAAAUAAAAGAAUUUU	2051
7203	AGGUCUUUCAGCUAUAAUG	401	7203	AGGUCUUUCAGCUAUAAUG	401	7221	CAUUAUAGCUGAAAGACCU	2052
7221	GCAGGUGUUCUUUGGCUAU	402	7221	GCAGGUGUUCUUUGGCUAU	402	7239	AUAGCCAAAGAACACCUGC	2053
7239	UUUUGCUAGUCAUUUCAUC	403	7239	UUUUGCUAGUCAUUUCAUC	403	7257	GAUGAAAUGACUAGCAAAA	2054
7257	CAGCAAUUCUUGGCUCAUG	404	7257	CAGCAAUUCUUGGCUCAUG	404	7275	CAUGAGCCAAGAAUUGCUG	2055
7275	GUGGUUUAUCAUUAGUAUU	405	7275	GUGGUUUAUCAUUAGUAUU	405	7293	AAUACUAAUGAUAAACCAC	2056
7293	UGUACAAAUGGCACCCGUU	406	7293	UGUACAAAUGGCACCCGUU	406	7311	AACGGGUGCCAUUUGUACA	2057
7311	UUCUGCAAUGGUUAGGAUG	407	7311	UUCUGCAAUGGUUAGGAUG	407	7329	CAUCCUAACCAUUGCAGAA	2058
7329	GUACAUCUUCUUUGCUUCU	408	7329	GUACAUCUUCUUUGCUUCU	408	7347	AGAAGCAAAGAAGAUGUAC	2059
7347	UUUCUACUACAUAUGGAAG	409	7347	UUUCUACUACAUAUGGAAG	409	7365	CUUCCAUAUGUAGUAGAAA	2060
7365	GAGCUAUGUUCAUAUCAUG	410	7365	GAGCUAUGUUCAUAUCAUG	410	7383	CAUGAUAUGAACAUAGCUC	2061
7383	GGAUGGUUGCACCUCUUCG	411	7383	GGAUGGUUGCACCUCUUCG	411	7401	CGAAGAGGUGCAACCAUCC	2062
7401	GACUUGCAUGAUGUGCUAU	412	7401	GACUUGCAUGAUGUGCUAU	412	7419	AUAGCACAUCAUGCAAGUC	2063
7419	UAAGCGCAAUCGUGCCACA	413	7419	UAAGCGCAAUCGUGCCACA	413	7437	UGUGGCACGAUUGCGCUUA	2064
7437	ACGCGUUGAGUGUACAACU	414	7437	ACGCGUUGAGUGUACAACU	414	7455	AGUUGUACACUCAACGCGU	2065

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7455	UAUUGUUAAUGGCAUGAAG	415	7455	UAUUGUUAAUGGCAUGAAG	415	7473	CUUCAUGCCAUUAACAAUA	2066
7473	GAGAUCUUUCUAUGUCUAU	416	7473	GAGAUCUUUCUAUGUCUAU	416	7491	AUAGACAUAGAAAGAUCUC	2067
7491	UGCAAAUGGAGGCCGUGGC	417	7491	UGCAAAUGGAGGCCGUGGC	417	7509	GCCACGGCCUCCAUUUGCA	2068
7509	CUUCUGCAAGACUCACAAU	418	7509	CUUCUGCAAGACUCACAAU	418	7527	AUUGUGAGUCUUGCAGAAG	2069
7527	UUGGAAUUGUCUCAAUUGU	419	7527	UUGGAAUUGUCUCAAUUGU	419	7545	ACAAUUGAGACAAUUCCAA	2070
7545	UGACACAUUUUGCACUGGU	420	7545	UGACACAUUUUGCACUGGU	420	7563	ACCAGUGCAAAAUGUGUCA	2071
7563	UAGUACAUUCAUUAGUGAU	421	7563	UAGUACAUUCAUUAGUGAU	421	7581	AUCACUAAUGAAUGUACUA	2072
7581	UGAAGUUGCUCGUGAUUUG	422	7581	UGAAGUUGCUCGUGAUUUG	422	7599	CAAAUCACGAGCAACUUCA	2073
7599	GUCACUCCAGUUUAAAAGA	423	7599	GUCACUCCAGUUUAAAAGA	423	7617	UCUUUUAAACUGGAGUGAC	2074
7617	ACCAAUCAACCCUACUGAC	424	7617	ACCAAUCAACCCUACUGAC	424	7635	GUCAGUAGGGUUGAUUGGU	2075
7635	CCAGUCAUCGUAUAUUGUU	425	7635	CCAGUCAUCGUAUAUUGUU	425	7653	AACAAUAUACGAUGACUGG	2076
7653	UGAUAGUGUUGCUGUGAAA	426	7653	UGAUAGUGUUGCUGUGAAA	426	7671	UUUCACAGCAACACUAUCA	2077
7671	AAAUGGCGCGCUUCACCUC	427	7671	AAAUGGCGCGCUUCACCUC	427	7689	GAGGUGAAGCGCGCCAUUU	2078
7689	CUACUUUGACAAGGCUGGU	428	7689	CUACUUUGACAAGGCUGGU	428	7707	ACCAGCCUUGUCAAAGUAG	2079
7707	UCAAAAGACCUAUGAGAGA	429	7707	UCAAAAGACCUAUGAGAGA	429	7725	UCUCUCAUAGGUCUUUUGA	2080
7725	ACAUCCGCUCUCCCAUUUU	430	7725	ACAUCCGCUCUCCCAUUUU	430	7743	AAAAUGGGAGAGCGGAUGU	2081
7743	UGUCAAUUUAGACAAUUUG	431	7743	UGUCAAUUUAGACAAUUUG	431	7761	CAAAUUGUCUAAAUUGACA	2082
7761	GAGAGCUAACAACACUAAA	432	7761	GAGAGCUAACAACACUAAA	432	7779	UUUAGUGUUGUUAGCUCUC	2083
7779	AGGUUCACUGCCUAUUAAU	433	7779	AGGUUCACUGCCUAUUAAU	433	7797	AUUAAUAGGCAGUGAACCU	2084
7797	UGUCAUAGUUUUUGAUGGC	434	7797	UGUCAUAGUUUUUGAUGGC	434	7815	GCCAUCAAAAACUAUGACA	2085
7815	CAAGUCCAAAUGCGACGAG	435	7815	CAAGUCCAAAUGCGACGAG	435	7833	CUCGUCGCAUUUGGACUUG	2086
7833	GUCUGCUUCUAAGUCUGCU	436	7833	GUCUGCUUCUAAGUCUGCU	436	7851	AGCAGACUUAGAAGCAGAC	2087
7851	UUCUGUGUACUACAGUCAG	437	7851	UUCUGUGUACUACAGUCAG	437	7869	CUGACUGUAGUACACAGAA	2088
7869	GCUGAUGUGCCAACCUAUU	438	7869	GCUGAUGUGCCAACCUAUU	438	7887	AAUAGGUUGGCACAUCAGC	2089
7887	UCUGUUGCUUGACCAAGCU	439	7887	UCUGUUGCUUGACCAAGCU	439	7905	AGCUUGGUCAAGCAACAGA	2090
7905	UCUUGUAUCAGACGUUGGA	440	7905	UCUUGUAUCAGACGUUGGA	440	7923	UCCAACGUCUGAUACAAGA	2091
7923	AGAUAGUACUGAAGUUUCC	441	7923	AGAUAGUACUGAAGUUUCC	441	7941	GGAAACUUCAGUACUAUCU	2092
7941	CGUUAAGAUGUUUGAUGCU	442	7941	CGUUAAGAUGUUUGAUGCU	442	7959	AGCAUCAAACAUCUUAACG	2093
7959	UUAUGUCGACACCUUUUCA	443	7959	UUAUGUCGACACCUUUUCA	443	7977	UGAAAAGGUGUCGACAUAA	2094
7977	AGCAACUUUUAGUGUUCCU	444	7977	AGCAACUUUUAGUGUUCCU	444	7995	AGGAACACUAAAAGUUGCU	2095
7995	UAUGGAAAAACUUAAGGCA	445	7995	UAUGGAAAAACUUAAGGCA	445	8013	UGCCUUAAGUUUUUCCAUA	2096
8013	ACUUGUUGCUACAGCUCAC	446	8013	ACUUGUUGCUACAGCUCAC	446	8031	GUGAGCUGUAGCAACAAGU	2097
8031	CAGCGAGUUAGCAAAGGGU	447	8031	CAGCGAGUUAGCAAAGGGU	447	8049	ACCCUUUGCUAACUCGCUG	2098
8049	UGUAGCUUUAGAUGGUGUC	448	8049	UGUAGCUUUAGAUGGUGUC	448	8067	GACACCAUCUAAAGCUACA	2099
8067	CCUUUCUACAUUCGUGUCA	449	8067	CCUUUCUACAUUCGUGUCA	449	8085	UGACACGAAUGUAGAAAGG	2100
8085	AGCUGCCCGACAAGGUGUU	450	8085	AGCUGCCCGACAAGGUGUU	450	8103	AACACCUUGUCGGGCAGCU	2101
8103	UGUUGAUACCGAUGUUGAC	451	8103	UGUUGAUACCGAUGUUGAC	451	8121	GUCAACAUCGGUAUCAACA	2102
8121	CACAAAGGAUGUUAUUGAA	452	8121	CACAAAGGAUGUUAUUGAA	452	8139	UUCAAUAACAUCCUUUGUG	2103
8139	AUGUCUCAAACUUUCACAU	453	8139	AUGUCUCAAACUUUCACAU	453	8157	AUGUGAAAGUUUGAGACAU	2104
8157	UCACUCUGACUUAGAAGUG	454	8157	UCACUCUGACUUAGAAGUG	454	8175	CACUUCUAAGUCAGAGUGA	2105
8175	GACAGGUGACAGUUGUAAC	455	8175	GACAGGUGACAGUUGUAAC	455	8193	GUUACAACUGUCACCUGUC	2106
8193	CAAUUUCAUGCUCACCUAU	456	8193	CAAUUUCAUGCUCACCUAU	456	8211	AUAGGUGAGCAUGAAAUUG	2107

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8211	UAAUAAGGUUGAAAACAUG	457	8211	UAAUAAGGUUGAAAACAUG	457	8229	CAUGUUUUCAACCUUAUUA	2108
8229	GACGCCCAGAGAUCUUGGC	458	8229	GACGCCCAGAGAUCUUGGC	458	8247	GCCAAGAUCUCUGGGCGUC	2109
8247	CGCAUGUAUUGACUGUAAU	459	8247	CGCAUGUAUUGACUGUAAU	459	8265	AUUACAGUCAAUACAUGCG	2110
8265	UGCAAGGCAUAUCAAUGCC	460	8265	UGCAAGGCAUAUCAAUGCC	460	8283	GGCAUUGAUAUGCCUUGCA	2111
8283	CCAAGUAGCAAAAAGUCAC	461	8283	CCAAGUAGCAAAAAGUCAC	461	8301	GUGACUUUUUGCUACUUGG	2112
8301	CAAUGUUUCACUCAUCUGG	462	8301	CAAUGUUUCACUCAUCUGG	462	8319	CCAGAUGAGUGAAACAUUG	2113
8319	GAAUGUAAAAGACUACAUG	463	8319	GAAUGUAAAAGACUACAUG	463	8337	CAUGUAGUCUUUUACAUUC	2114
8337	GUCUUUAUCUGAACAGCUG	464	8337	GUCUUUAUCUGAACAGCUG	464	8355	CAGCUGUUCAGAUAAAGAC	2115
8355	GCGUAAACAAAUUCGUAGU	465	8355	GCGUAAACAAAUUCGUAGU	465	8373	ACUACGAAUUUGUUUACGC	2116
8373	UGCUGCCAAGAAGAACAAC	466	8373	UGCUGCCAAGAAGAACAAC	466	8391	GUUGUUCUUCUUGGCAGCA	2117
8391	CAUACCUUUUAGACUAACU	467	8391	CAUACCUUUUAGACUAACU	467	8409	AGUUAGUCUAAAAGGUAUG	2118
8409	UUGUGCUACAACUAGACAG	468	8409	UUGUGCUACAACUAGACAG	468	8427	CUGUCUAGUUGUAGCACAA	2119
8427	GGUUGUCAAUGUCAUAACU	469	8427	GGUUGUCAAUGUCAUAACU	469	8445	AGUUAUGACAUUGACAACC	2120
8445	UACUAAAAUCUCACUCAAG	470	8445	UACUAAAAUCUCACUCAAG	470	8463	CUUGAGUGAGAUUUUAGUA	2121
8463	GGGUGGUAAGAUUGUUAGU	471	8463	GGGUGGUAAGAUUGUUAGU	471	8481	ACUAACAAUCUUACCACCC	2122
8481	UACUUGUUUUAAACUUAUG	472	8481	UACUUGUUUUAAACUUAUG	472	8499	CAUAAGUUUAAAACAAGUA	2123
8499	GCUUAAGGCCACAUUAUUG	473	8499	GCUUAAGGCCACAUUAUUG	473	8517	CAAUAAUGUGGCCUUAAGC	2124
8517	GUGCGUUCUUGCUGCAUUG	474	8517	GUGCGUUCUUGCUGCAUUG	474	8535	CAAUGCAGCAAGAACGCAC	2125
8535	GGUUUGUUAUAUCGUUAUG	475	8535	GGUUUGUUAUAUCGUUAUG	475	8553	CAUAACGAUAUAACAAACC	2126
8553	GCCAGUACAUACAUUGUCA	476	8553	GCCAGUACAUACAUUGUCA	476	8571	UGACAAUGUAUGUACUGGC	2127
8571	AAUCCAUGAUGGUUACACA	477	8571	AAUCCAUGAUGGUUACACA	477	8589	UGUGUAACCAUCAUGGAUU	2128
8589	AAAUGAAAUCAUUGGUUAC	478	8589	AAAUGAAAUCAUUGGUUAC	478	8607	GUAACCAAUGAUUUCAUUU	2129
8607	CAAAGCCAUUCAGGAUGGU	479	8607	CAAAGCCAUUCAGGAUGGU	479	8625	ACCAUCCUGAAUGGCUUUG	2130
8625	UGUCACUCGUGACAUCAUU	480	8625	UGUCACUCGUGACAUCAUU	480	8643	AAUGAUGUCACGAGUGACA	2131
8643	UUCUACUGAUGAUUGUUUU	481	8643	UUCUACUGAUGAUUGUUUU	481	8661	AAAACAAUCAUCAGUAGAA	2132
8661	UGCAAAUAAACAUGCUGGU	482	8661	UGCAAAUAAACAUGCUGGU	482	8679	ACCAGCAUGUUUAUUUGCA	2133
8679	UUUUGACGCAUGGUUUAGC	483	8679	UUUUGACGCAUGGUUUAGC	483	8697	GCUAAACCAUGCGUCAAAA	2134
8697	CCAGCGUGGUGGUUCAUAC	484	8697	CCAGCGUGGUGGUUCAUAC	484	8715	GUAUGAACCACCACGCUGG	2135
8715	CAAAAAUGACAAAAGCUGC	485	8715	CAAAAAUGACAAAAGCUGC	485	8733	GCAGCUUUUGUCAUUUUUG	2136
8733	CCCUGUAGUAGCUGCUAUC	486	8733	CCCUGUAGUAGCUGCUAUC	486	8751	GAUAGCAGCUACUACAGGG	2137
8751	CAUUACAAGAGAGAUUGGU	487	8751	CAUUACAAGAGAGAUUGGU	487	8769	ACCAAUCUCUCUUGUAAUG	2138
8769	UUUCAUAGUGCCUGGCUUA	488	8769	UUUCAUAGUGCCUGGCUUA	488	8787	UAAGCCAGGCACUAUGAAA	2139
8787	ACCGGGUACUGUGCUGAGA	489	8787	ACCGGGUACUGUGCUGAGA	489	8805	UCUCAGCACAGUACCCGGU	2140
8805	AGCAAUCAAUGGUGACUUC	490	8805	AGCAAUCAAUGGUGACUUC	490	8823	GAAGUCACCAUUGAUUGCU	2141
8823	CUUGCAUUUUCUACCUCGU	491	8823	CUUGCAUUUUCUACCUCGU	491	8841	ACGAGGUAGAAAAUGCAAG	2142
8841	UGUUUUUAGUGCUGUUGGC	492	8841	UGUUUUUAGUGCUGUUGGC	492	8859	GCCAACAGCACUAAAAACA	2143
8859	CAACAUUUGCUACACACCU	493	8859	CAACAUUUGCUACACACCU	493	8877	AGGUGUGUAGCAAAUGUUG	2144
8877	UUCCAAACUCAUUGAGUAU	494	8877	UUCCAAACUCAUUGAGUAU	494	8895	AUACUCAAUGAGUUUGGAA	2145
8895	UAGUGAUUUUGCUACCUCU	495	8895	UAGUGAUUUUGCUACCUCU	495	8913	AGAGGUAGCAAAAUCACUA	2146
8913	UGCUUGCGUUCUUGCUGCU	496	8913	UGCUUGCGUUCUUGCUGCU	496	8931	AGCAGCAAGAACGCAAGCA	2147
8931	UGAGUGUACAAUUUUUAAG	497	8931	UGAGUGUACAAUUUUUAAG	497	8949	CUUAAAAAUUGUACACUCA	2148
8949	GGAUGCUAUGGGCAAACCU	498	8949	GGAUGCUAUGGGCAAACCU	498	8967	AGGUUUGCCCAUAGCAUCC	2149

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8967	UGUGCCAUAUUGUUAUGAC	499	8967	UGUGCCAUAUUGUUAUGAC	499	8985	GUCAUAACAAUAUGGCACA	2150
8985	CACUAAUUUGCUAGAGGGU	500	8985	CACUAAUUUGCUAGAGGGU	500	9003	ACCCUCUAGCAAAUUAGUG	2151
9003	UUCUAUUUCUUAUAGUGAG	501	9003	UUCUAUUUCUUAUAGUGAG	501	9021	CUCACUAUAAGAAAUAGAA	2152
9021	GCUUCGUCCAGACACUCGU	502	9021	GCUUCGUCCAGACACUCGU	502	9039	ACGAGUGUCUGGACGAAGC	2153
9039	UUAUGUGCUUAUGGAUGGU	503	9039	UUAUGUGCUUAUGGAUGGU	503	9057	ACCAUCCAUAAGCACAUAA	2154
9057	UUCCAUCAUACAGUUUCCU	504	9057	UUCCAUCAUACAGUUUCCU	504	9075	AGGAAACUGUAUGAUGGAA	2155
9075	UAACACUUACCUGGAGGGU	505	9075	UAACACUUACCUGGAGGGU	505	9093	ACCCUCCAGGUAAGUGUUA	2156
9093	UUCUGUUAGAGUAGUAACA	506	9093	UUCUGUUAGAGUAGUAACA	506	9111	UGUUACUACUCUAACAGAA	2157
9111	AACUUUUGAUGCUGAGUAC	507	9111	AACUUUUGAUGCUGAGUAC	507	9129	GUACUCAGCAUCAAAAGUU	2158
9129	CUGUAGACAUGGUACAUGC	508	9129	CUGUAGACAUGGUACAUGC	508	9147	GCAUGUACCAUGUCUACAG	2159
9147	CGAAAGGUCAGAAGUAGGU	509	9147	CGAAAGGUCAGAAGUAGGU	509	9165	ACCUACUUCUGACCUUUCG	2160
9165	UAUUUGCCUAUCUACCAGU	510	9165	UAUUUGCCUAUCUACCAGU	510	9183	ACUGGUAGAUAGGCAAAUA	2161
9183	UGGUAGAUGGGUUCUUAAU	511	9183	UGGUAGAUGGGUUCUUAAU	511	9201	AUUAAGAACCCAUCUACCA	2162
9201	UAAUGAGCAUUACAGAGCU	512	9201	UAAUGAGCAUUACAGAGCU	512	9219	AGCUCUGUAAUGCUCAUUA	2163
9219	UCUAUCAGGAGUUUUCUGU	513	9219	UCUAUCAGGAGUUUUCUGU	513	9237	ACAGAAAACUCCUGAUAGA	2164
9237	UGGUGUUGAUGCGAUGAAU	514	9237	UGGUGUUGAUGCGAUGAAU	514	9255	AUUCAUCGCAUCAACACCA	2165
9255	UCUCAUAGCUAACAUCUUU	515	9255	UCUCAUAGCUAACAUCUUU	515	9273	AAAGAUGUUAGCUAUGAGA	2166
9273	UACUCCUCUUGUGCAACCU	516	9273	UACUCCUCUUGUGCAACCU	516	9291	AGGUUGCACAAGAGGAGUA	2167
9291	UGUGGGUGCUUUAGAUGUG	517	9291	UGUGGGUGCUUUAGAUGUG	517	9309	CACAUCUAAAGCACCCACA	2168
9309	GUCUGCUUCAGUAGUGGCU	518	9309	GUCUGCUUCAGUAGUGGCU	518	9327	AGCCACUACUGAAGCAGAC	2169
9327	UGGUGGUAUUAUUGCCAUA	519	9327	UGGUGGUAUUAUUGCCAUA	519	9345	UAUGGCAAUAAUACCACCA	2170
9345	AUUGGUGACUUGUGCUGCC	520	9345	AUUGGUGACUUGUGCUGCC	520	9363	GGCAGCACAAGUCACCAAU	2171
9363	CUACUACUUUAUGAAAUUC	521	9363	CUACUACUUUAUGAAAUUC	521	9381	GAAUUUCAUAAAGUAGUAG	2172
9381	CAGACGUGUUUUUGGUGAG	522	9381	CAGACGUGUUUUUGGUGAG	522	9399	CUCACCAAAAACACGUCUG	2173
9399	GUACAACCAUGUUGUUGCU	523	9399	GUACAACCAUGUUGUUGCU	523	9417	AGCAACAACAUGGUUGUAC	2174
9417	UGCUAAUGCACUUUUGUUU	524	9417	UGCUAAUGCACUUUUGUUU	524	9435	AAACAAAAGUGCAUUAGCA	2175
9435	UUUGAUGUCUUUCACUAUA	525	9435	UUUGAUGUCUUUCACUAUA	525	9453	UAUAGUGAAAGACAUCAAA	2176
9453	ACUCUGUCUGGUACCAGCU	526	9453	ACUCUGUCUGGUACCAGCU	526	9471	AGCUGGUACCAGACAGAGU	2177
9471	UUACAGCUUUCUGCCGGGA	527	9471	UUACAGCUUUCUGCCGGGA	527	9489	UCCCGGCAGAAAGCUGUAA	2178
9489	AGUCUACUCAGUCUUUUAC	528	9489	AGUCUACUCAGUCUUUUAC	528	9507	GUAAAAGACUGAGUAGACU	2179
9507	CUUGUACUUGACAUUCUAU	529	9507	CUUGUACUUGACAUUCUAU	529	9525	AUAGAAUGUCAAGUACAAG	2180
9525	UUUCACCAAUGAUGUUUCA	530	9525	UUUCACCAAUGAUGUUUCA	530	9543	UGAAACAUCAUUGGUGAAA	2181
9543	AUUCUUGGCUCACCUUCAA	531	9543	AUUCUUGGCUCACCUUCAA	531	9561	UUGAAGGUGAGCCAAGAAU	2182
9561	AUGGUUUGCCAUGUUUUCU	532	9561	AUGGUUUGCCAUGUUUUCU	532	9579	AGAAAACAUGGCAAACCAU	2183
9579	UCCUAUUGUGCCUUUUUGG	533	9579	UCCUAUUGUGCCUUUUUGG	533	9597	CCAAAAAGGCACAAUAGGA	2184
9597	GAUAACAGCAAUCUAUGUA	534	9597	GAUAACAGCAAUCUAUGUA	534	9615	UACAUAGAUUGCUGUUAUC	2185
9615	AUUCUGUAUUUCUCUGAAG	535	9615	AUUCUGUAUUUCUCUGAAG	535	9633	CUUCAGAGAAAUACAGAAU	2186
9633	GCACUGCCAUUGGUUCUUU	536	9633	GCACUGCCAUUGGUUCUUU	536	9651	AAAGAACCAAUGGCAGUGC	2187
9651	UAACAACUAUCUUAGGAAA	537	9651	UAACAACUAUCUUAGGAAA	537	9669	UUUCCUAAGAUAGUUGUUA	2188
9669	AAGAGUCAUGUUUAAUGGA	538	9669	AAGAGUCAUGUUUAAUGGA	538	9687	UCCAUUAAACAUGACUCUU	2189
9687	AGUUACAUUUAGUACCUUC	539	9687	AGUUACAUUUAGUACCUUC	539	9705	GAAGGUACUAAAUGUAACU	2190
9705	CGAGGAGGCUGCUUUGUGU	540	9705	CGAGGAGGCUGCUUUGUGU	540	9723	ACACAAAGCAGCCUCCUCG	2191

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9723	UACCUUUUUGCUCAACAAG	541	9723	UACCUUUUUGCUCAACAAG	541	9741	CUUGUUGAGCAAAAAGGUA	2192
9741	GGAAAUGUACCUAAAAUUG	542	9741	GGAAAUGUACCUAAAAUUG	542	9759	CAAUUUUAGGUACAUUUCC	2193
9759	GCGUAGCGAGACACUGUUG	543	9759	GCGUAGCGAGACACUGUUG	543	9777	CAACAGUGUCUCGCUACGC	2194
9777	GCCACUUACACAGUAUAAC	544	9777	GCCACUUACACAGUAUAAC	544	9795	GUUAUACUGUGUAAGUGGC	2195
9795	CAGGUAUCUUGCUCUAUAU	545	9795	CAGGUAUCUUGCUCUAUAU	545	9813	AUAUAGAGCAAGAUACCUG	2196
9813	UAACAAGUACAAGUAUUUC	546	9813	UAACAAGUACAAGUAUUUC	546	9831	GAAAUACUUGUACUUGUUA	2197
9831	CAGUGGAGCCUUAGAUACU	547	9831	CAGUGGAGCCUUAGAUACU	547	9849	AGUAUCUAAGGCUCCACUG	2198
9849	UACCAGCUAUCGUGAAGCA	548	9849	UACCAGCUAUCGUGAAGCA	548	9867	UGCUUCACGAUAGCUGGUA	2199
9867	AGCUUGCUGCCACUUAGCA	549	9867	AGCUUGCUGCCACUUAGCA	549	9885	UGCUAAGUGGCAGCAAGCU	2200
9885	AAAGGCUCUAAAUGACUUU	550	9885	AAAGGCUCUAAAUGACUUU	550	9903	AAAGUCAUUUAGAGCCUUU	2201
9903	UAGCAACUCAGGUGCUGAU	551	9903	UAGCAACUCAGGUGCUGAU	551	9921	AUCAGCACCUGAGUUGCUA	2202
9921	UGUUCUCUACCAACCACCA	552	9921	UGUUCUCUACCAACCACCA	552	9939	UGGUGGUUGGUAGAGAACA	2203
9939	ACAGACAUCAAUCACUUCU	553	9939	ACAGACAUCAAUCACUUCU	553	9957	AGAAGUGAUUGAUGUCUGU	2204
9957	UGCUGUUCUGCAGAGUGGU	554	9957	UGCUGUUCUGCAGAGUGGU	554	9975	ACCACUCUGCAGAACAGCA	2205
9975	UUUUAGGAAAAUGGCAUUC	555	9975	UUUUAGGAAAAUGGCAUUC	555	9993	GAAUGCCAUUUUCCUAAAA	2206
9993	CCCGUCAGGCAAAGUUGAA	556	9993	CCCGUCAGGCAAAGUUGAA	556	10011	UUCAACUUUGCCUGACGGG	2207
10011	AGGGUGCAUGGUACAAGUA	557	10011	AGGGUGCAUGGUACAAGUA	557	10029	UACUUGUACCAUGCACCCU	2208
10029	AACCUGUGGAACUACAACU	558	10029	AACCUGUGGAACUACAACU	558	10047	AGUUGUAGUUCCACAGGUU	2209
10047	UCUUAAUGGAUUGUGGUUG	559	10047	UCUUAAUGGAUUGUGGUUG	559	10065	CAACCACAAUCCAUUAAGA	2210
10065	GGAUGACACAGUAUACUGU	560	10065	GGAUGACACAGUAUACUGU	560	10083	ACAGUAUACUGUGUCAUCC	2211
10083	UCCAAGACAUGUCAUUUGC	561	10083	UCCAAGACAUGUCAUUUGC	561	10101	GCAAAUGACAUGUCUUGGA	2212
10101	CACAGCAGAAGACAUGCUU	562	10101	CACAGCAGAAGACAUGCUU	562	10119	AAGCAUGUCUUCUGCUGUG	2213
10119	UAAUCCUAACUAUGAAGAU	563	10119	UAAUCCUAACUAUGAAGAU	563	10137	AUCUUCAUAGUUAGGAUUA	2214
10137	UCUGCUCAUUCGCAAAUCC	564	10137	UCUGCUCAUUCGCAAAUCC	564	10155	GGAUUUGCGAAUGAGCAGA	2215
10155	CAACCAUAGCUUUCUUGUU	565	10155	CAACCAUAGCUUUCUUGUU	565	10173	AACAAGAAAGCUAUGGUUG	2216
10173	UCAGGCUGGCAAUGUUCAA	566	10173	UCAGGCUGGCAAUGUUCAA	566	10191	UUGAACAUUGCCAGCCUGA	2217
10191	ACUUCGUGUUAUUGGCCAU	567	10191	ACUUCGUGUUAUUGGCCAU	567	10209	AUGGCCAAUAACACGAAGU	2218
10209	UUCUAUGCAAAAUUGUCUG	568	10209	UUCUAUGCAAAAUUGUCUG	568	10227	CAGACAAUUUUGCAUAGAA	2219
10227	GCUUAGGCUUAAAGUUGAU	569	10227	GCUUAGGCUUAAAGUUGAU	569	10245	AUCAACUUUAAGCCUAAGC	2220
10245	UACUUCUAACCCUAAGACA	570	10245	UACUUCUAACCCUAAGACA	570	10263	UGUCUUAGGGUUAGAAGUA	2221
10263	ACCCAAGUAUAAAUUUGUC	571	10263	ACCCAAGUAUAAAUUUGUC	571	10281	GACAAAUUUAUACUUGGGU	2222
10281	CCGUAUCCAACCUGGUCAA	572	10281	CCGUAUCCAACCUGGUCAA	572	10299	UUGACCAGGUUGGAUACGG	2223
10299	AACAUUUUCAGUUCUAGCA	573	10299	AACAUUUUCAGUUCUAGCA	573	10317	UGCUAGAACUGAAAAUGUU	2224
10317	AUGCUACAAUGGUUCACCA	574	10317	AUGCUACAAUGGUUCACCA	574	10335	UGGUGAACCAUUGUAGCAU	2225
10335	AUCUGGUGUUUAUCAGUGU	575	10335	AUCUGGUGUUUAUCAGUGU	575	10353	ACACUGAUAAACACCAGAU	2226
10353	UGCCAUGAGACCUAAUCAU	576	10353	UGCCAUGAGACCUAAUCAU	576	10371	AUGAUUAGGUCUCAUGGCA	2227
10371	UACCAUUAAAGGUUCUUUC	577	10371	UACCAUUAAAGGUUCUUUC	577	10389	GAAAGAACCUUUAAUGGUA	2228
10389	CCUUAAUGGAUCAUGUGGU	578	10389	CCUUAAUGGAUCAUGUGGU	578	10407	ACCACAUGAUCCAUUAAGG	2229
10407	UAGUGUUGGUUUUAACAUU	579	10407	UAGUGUUGGUUUUAACAUU	579	10425	AAUGUUAAAACCAACACUA	2230
10425	UGAUUAUGAUUGCGUGUCU	580	10425	UGAUUAUGAUUGCGUGUCU	580	10443	AGACACGCAAUCAUAAUCA	2231
10443	UUUCUGCUAUAUGCAUCAU	581	10443	UUUCUGCUAUAUGCAUCAU	581	10461	AUGAUGCAUAUAGCAGAAA	2232
10461	UAUGGAGCUUCCAACAGGA	582	10461	UAUGGAGCUUCCAACAGGA	582	10479	UCCUGUUGGAAGCUCCAUA	2233

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10479	AGUACACGCUGGUACUGAC	583	10479	AGUACACGCUGGUACUGAC	583	10497	GUCAGUACCAGCGUGUACU	2234
10497	CUUAGAAGGUAAAUUCUAU	584	10497	CUUAGAAGGUAAAUUCUAU	584	10515	AUAGAAUUUACCUUCUAAG	2235
10515	UGGUCCAUUUGUUGACAGA	585	10515	UGGUCCAUUUGUUGACAGA	585	10533	UCUGUCAACAAAUGGACCA	2236
10533	ACAAACUGCACAGGCUGCA	586	10533	ACAAACUGCACAGGCUGCA	586	10551	UGCAGCCUGUGCAGUUUGU	2237
10551	AGGUACAGACACAACCAUA	587	10551	AGGUACAGACACAACCAUA	587	10569	UAUGGUUGUGUCUGUACCU	2238
10569	AACAUUAAAUGUUUUGGCA	588	10569	AACAUUAAAUGUUUUGGCA	588	10587	UGCCAAAACAUUUAAUGUU	2239
10587	AUGGCUGUAUGCUGCUGUU	589	10587	AUGGCUGUAUGCUGCUGUU	589	10605	AACAGCAGCAUACAGCCAU	2240
10605	UAUCAAUGGUGAUAGGUGG	590	10605	UAUCAAUGGUGAUAGGUGG	590	10623	CCACCUAUCACCAUUGAUA	2241
10623	GUUUCUUAAUAGAUUCACC	591	10623	GUUUCUUAAUAGAUUCACC	591	10641	GGUGAAUCUAUUAAGAAAC	2242
10641	CACUACUUUGAAUGACUUU	592	10641	CACUACUUUGAAUGACUUU	592	10659	AAAGUCAUUCAAAGUAGUG	2243
10659	UAACCUUGUGGCAAUGAAG	593	10659	UAACCUUGUGGCAAUGAAG	593	10677	CUUCAUUGCCACAAGGUUA	2244
10677	GUACAACUAUGAACCUUUG	594	10677	GUACAACUAUGAACCUUUG	594	10695	CAAAGGUUCAUAGUUGUAC	2245
10695	GACACAAGAUCAUGUUGAC	595	10695	GACACAAGAUCAUGUUGAC	595	10713	GUCAACAUGAUCUUGUGUC	2246
10713	CAUAUUGGGACCUCUUUCU	596	10713	CAUAUUGGGACCUCUUUCU	596	10731	AGAAAGAGGUCCCAAUAUG	2247
10731	UGCUCAAACAGGAAUUGCC	597	10731	UGCUCAAACAGGAAUUGCC	597	10749	GGCAAUUCCUGUUUGAGCA	2248
10749	CGUCUUAGAUAUGUGUGCU	598	10749	CGUCUUAGAUAUGUGUGCU	598	10767	AGCACACAUAUCUAAGACG	2249
10767	UGCUUUGAAAGAGCUGCUG	599	10767	UGCUUUGAAAGAGCUGCUG	599	10785	CAGCAGCUCUUUCAAAGCA	2250
10785	GCAGAAUGGUAUGAAUGGU	600	10785	GCAGAAUGGUAUGAAUGGU	600	10803	ACCAUUCAUACCAUUCUGC	2251
10803	UCGUACUAUCCUUGGUAGC	601	10803	UCGUACUAUCCUUGGUAGC	601	10821	GCUACCAAGGAUAGUACGA	2252
10821	CACUAUUUUAGAAGAUGAG	602	10821	CACUAUUUUAGAAGAUGAG	602	10839	CUCAUCUUCUAAAAUAGUG	2253
10839	GUUUACACCAUUUGAUGUU	603	10839	GUUUACACCAUUUGAUGUU	603	10857	AACAUCAAAUGGUGUAAAC	2254
10857	UGUUAGACAAUGCUCUGGU	604	10857	UGUUAGACAAUGCUCUGGU	604	10875	ACCAGAGCAUUGUCUAACA	2255
10875	UGUUACCUUCCAAGGUAAG	605	10875	UGUUACCUUCCAAGGUAAG	605	10893	CUUACCUUGGAAGGUAACA	2256
10893	GUUCAAGAAAAUUGUUAAG	606	10893	GUUCAAGAAAAUUGUUAAG	606	10911	CUUAACAAUUUUCUUGAAC	2257
10911	GGGCACUCAUCAUUGGAUG	607	10911	GGGCACUCAUCAUUGGAUG	607	10929	CAUCCAAUGAUGAGUGCCC	2258
10929	GCUUUUAACUUUCUUGACA	608	10929	GCUUUUAACUUUCUUGACA	608	10947	UGUCAAGAAAGUUAAAAGC	2259
10947	AUCACUAUUGAUUCUUGUU	609	10947	AUCACUAUUGAUUCUUGUU	609	10965	AACAAGAAUCAAUAGUGAU	2260
10965	UCAAAGUACACAGUGGUCA	610	10965	UCAAAGUACACAGUGGUCA	610	10983	UGACCACUGUGUACUUUGA	2261
10983	ACUGUUUUUCUUUGUUUAC	611	10983	ACUGUUUUUCUUUGUUUAC	611	11001	GUAAACAAAGAAAAACAGU	2262
11001	CGAGAAUGCUUUCUUGCCA	612	11001	CGAGAAUGCUUUCUUGCCA	612	11019	UGGCAAGAAAGCAUUCUCG	2263
11019	AUUUACUCUUGGUAUUAUG	613	11019	AUUUACUCUUGGUAUUAUG	613	11037	CAUAAUACCAAGAGUAAAU	2264
11037	GGCAAUUGCUGCAUGUGCU	614	11037	GGCAAUUGCUGCAUGUGCU	614	11055	AGCACAUGCAGCAAUUGCC	2265
11055	UAUGCUGCUUGUUAAGCAU	615	11055	UAUGCUGCUUGUUAAGCAU	615	11073	AUGCUUAACAAGCAGCAUA	2266
11073	UAAGCACGCAUUCUUGUGC	616	11073	UAAGCACGCAUUCUUGUGC	616	11091	GCACAAGAAUGCGUGCUUA	2267
11091	CUUGUUUCUGUUACCUUCU	617	11091	CUUGUUUCUGUUACCUUCU	617	11109	AGAAGGUAACAGAAACAAG	2268
11109	UCUUGCAACAGUUGCUUAC	618	11109	UCUUGCAACAGUUGCUUAC	618	11127	GUAAGCAACUGUUGCAAGA	2269
11127	CUUUAAUAUGGUCUACAUG	619	11127	CUUUAAUAUGGUCUACAUG	619	11145	CAUGUAGACCAUAUUAAAG	2270
11145	GCCUGCUAGCUGGGUGAUG	620	11145	GCCUGCUAGCUGGGUGAUG	620	11163	CAUCACCCAGCUAGCAGGC	2271
11163	GCGUAUCAUGACAUGGCUU	621	11163	GCGUAUCAUGACAUGGCUU	621	11181	AAGCCAUGUCAUGAUACGC	2272
11181	UGAAUUGGCUGACACUAGC	622	11181	UGAAUUGGCUGACACUAGC	622	11199	GCUAGUGUCAGCCAAUUCA	2273
11199	CUUGUCUGGUUAUAGGCUU	623	11199	CUUGUCUGGUUAUAGGCUU	623	11217	AAGCCUAUAACCAGACAAG	2274
11217	UAAGGAUUGUGUUAUGUAU	624	11217	UAAGGAUUGUGUUAUGUAU	624	11235	AUACAUAACACAAUCCUUA	2275

11235	UGCUUCAGCUUUAGUUUUG	625	11235	UGCUUCAGCUUUAGUUUUG	625	11253	CAAAACUAAAGCUGAAGCA	2276
11253	GCUUAUUCUCAUGACAGCU	626	11253	GCUUAUUCUCAUGACAGCU	626	11271	AGCUGUCAUGAGAAUAAGC	2277
11271	UCGCACUGUUUAUGAUGAU	627	11271	UCGCACUGUUUAUGAUGAU	627	11289	AUCAUCAUAAACAGUGCGA	2278
11289	UGCUGCUAGACGUGUUUGG	628	11289	UGCUGCUAGACGUGUUUGG	628	11307	CCAAACACGUCUAGCAGCA	2279
11307	GACACUGAUGAAUGUCAUU	629	11307	GACACUGAUGAAUGUCAUU	629	11325	AAUGACAUUCAUCAGUGUC	2280
11325	UACACUUGUUUACAAAGUC	630	11325	UACACUUGUUUACAAAGUC	630	11343	GACUUUGUAAACAAGUGUA	2281
11343	CUACUAUGGUAAUGCUUUA	631	11343	CUACUAUGGUAAUGCUUUA	631	11361	UAAAGCAUUACCAUAGUAG	2282
11361	AGAUCAAGCUAUUUCCAUG	632	11361	AGAUCAAGCUAUUUCCAUG	632	11379	CAUGGAAAUAGCUUGAUCU	2283
11379	GUGGGCCUUAGUUAUUUCU	633	11379	GUGGGCCUUAGUUAUUUCU	633	11397	AGAAAUAACUAAGGCCCAC	2284
11397	UGUAACCUCUAACUAUUCU	634	11397	UGUAACCUCUAACUAUUCU	634	11415	AGAAUAGUUAGAGGUUACA	2285
11415	UGGUGUCGUUACGACUAUC	635	11415	UGGUGUCGUUACGACUAUC	635	11433	GAUAGUCGUAACGACACCA	2286
11433	CAUGUUUUUAGCUAGAGCU	636	11433	CAUGUUUUUAGCUAGAGCU	636	11451	AGCUCUAGCUAAAAACAUG	2287
11451	UAUAGUGUUUGUGUGUGUU	637	11451	UAUAGUGUUUGUGUGUGUU	637	11469	AACACACACAAACACUAUA	2288
11469	UGAGUAUUACCCAUUGUUA	638	11469	UGAGUAUUACCCAUUGUUA	638	11487	UAACAAUGGGUAAUACUCA	2289
11487	AUUUAUUACUGGCAACACC	639	11487	AUUUAUUACUGGCAACACC	639	11505	GGUGUUGCCAGUAAUAAAU	2290
11505	CUUACAGUGUAUCAUGCUU	640	11505	CUUACAGUGUAUCAUGCUU	640	11523	AAGCAUGAUACACUGUAAG	2291
11523	UGUUUAUUGUUUCUUAGGC	641	11523	UGUUUAUUGUUUCUUAGGC	641	11541	GCCUAAGAAACAAUAAACA	2292
11541	CUAUUGUUGCUGCUGCUAC	642	11541	CUAUUGUUGCUGCUGCUAC	642	11559	GUAGCAGCAGCAACAAUAG	2293
11559	CUUUGGCCUUUUCUGUUUA	643	11559	CUUUGGCCUUUUCUGUUUA	643	11577	UAAACAGAAAAGGCCAAAG	2294
11577	ACUCAACCGUUACUUCAGG	644	11577	ACUCAACCGUUACUUCAGG	644	11595	CCUGAAGUAACGGUUGAGU	2295
11595	GCUUACUCUUGGUGUUUAU	645	11595	GCUUACUCUUGGUGUUUAU	645	11613	AUAAACACCAAGAGUAAGC	2296
11613	UGACUACUUGGUCUCUACA	646	11613	UGACUACUUGGUCUCUACA	646	11631	UGUAGAGACCAAGUAGUCA	2297
11631	ACAAGAAUUUAGGUAUAUG	647	11631	ACAAGAAUUUAGGUAUAUG	647	11649	CAUAUACCUAAAUUCUUGU	2298
11649	GAACUCCCAGGGGCUUUUG	648	11649	GAACUCCCAGGGGCUUUUG	648	11667	CAAAAGCCCCUGGGAGUUC	2299
11667	GCCUCCUAAGAGUAGUAUU	649	11667	GCCUCCUAAGAGUAGUAUU	649	11685	AAUACUACUCUUAGGAGGC	2300
11685	UGAUGCUUUCAAGCUUAAC	650	11685	UGAUGCUUUCAAGCUUAAC	650	11703	GUUAAGCUUGAAAGCAUCA	2301
11703	CAUUAAGUUGUUGGGUAUU	651	11703	CAUUAAGUUGUUGGGUAUU	651	11721	AAUACCCAACAACUUAAUG	2302
11721	UGGAGGUAAACCAUGUAUC	652	11721	UGGAGGUAAACCAUGUAUC	652	11739	GAUACAUGGUUUACCUCCA	2303
11739	CAAGGUUGCUACUGUACAG	653	11739	CAAGGUUGCUACUGUACAG	653	11757	CUGUACAGUAGCAACCUUG	2304
11757	GUCUAAAAUGUCUGACGUA	654	11757	GUCUAAAAUGUCUGACGUA	654	11775	UACGUCAGACAUUUUAGAC	2305
11775	AAAGUGCACAUCUGUGGUA	655	11775	AAAGUGCACAUCUGUGGUA	655	11793	UACCACAGAUGUGCACUUU	2306
11793	ACUGCUCUCGGUUCUUCAA	656	11793	ACUGCUCUCGGUUCUUCAA	656	11811	UUGAAGAACCGAGAGCAGU	2307
11811	ACAACUUAGAGUAGAGUCA	657	11811	ACAACUUAGAGUAGAGUCA	657	11829	UGACUCUACUCUAAGUUGU	2308
11829	AUCUUCUAAAUUGUGGGCA	658	11829	AUCUUCUAAAUUGUGGGCA	658	11847	UGCCCACAAUUUAGAAGAU	2309
11847	ACAAUGUGUACAACUCCAC	659	11847	ACAAUGUGUACAACUCCAC	659	11865	GUGGAGUUGUACACAUUGU	2310
11865	CAAUGAUAUUCUUCUUGCA	660	11865	CAAUGAUAUUCUUCUUGCA	660	11883	UGCAAGAAGAAUAUCAUUG	2311
11883	AAAAGACACAACUGAAGCU	661	11883	AAAAGACACAACUGAAGCU	661	11901	AGCUUCAGUUGUGUCUUUU	2312
11901	UUUCGAGAAGAUGGUUUCU	662	11901	UUUCGAGAAGAUGGUUUCU	662	11919	AGAAACCAUCUUCUCGAAA	2313
11919	UCUUUUGUCUGUUUUGCUA	663	11919	UCUUUUGUCUGUUUUGCUA	663	11937	UAGCAAAACAGACAAAAGA	2314
11937	AUCCAUGCAGGGUGCUGUA	664	11937	AUCCAUGCAGGGUGCUGUA	664	11955	UACAGCACCCUGCAUGGAU	2315
11955	AGACAUUAAUAGGUUGUGC	665	11955	AGACAUUAAUAGGUUGUGC	665	11973	GCACAACCUAUUAAUGUCU	2316
11973	CGAGGAAAUGCUCGAUAAC	666	11973	CGAGGAAAUGCUCGAUAAC	666	11991	GUUAUCGAGCAUUUCCUCG	2317

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11991	CCGUGCUACUCUUCAGGCU	667	11991	CCGUGCUACUCUUCAGGCU	667	12009	AGCCUGAAGAGUAGCACGG	2318
12009	UAUUGCUUCAGAAUUUAGU	668	12009	UAUUGCUUCAGAAUUUAGU	668	12027	ACUAAAUUCUGAAGCAAUA	2319
12027	UUCUUUACCAUCAUAUGCC	669	12027	UUCUUUACCAUCAUAUGCC	669	12045	GGCAUAUGAUGGUAAAGAA	2320
12045	CGCUUAUGCCACUGCCCAG	670	12045	CGCUUAUGCCACUGCCCAG	670	12063	CUGGGCAGUGGCAUAAGCG	2321
12063	GGAGGCCUAUGAGCAGGCU	671	12063	GGAGGCCUAUGAGCAGGCU	671	12081	AGCCUGCUCAUAGGCCUCC	2322
12081	UGUAGCUAAUGGUGAUUCU	672	12081	UGUAGCUAAUGGUGAUUCU	672	12099	AGAAUCACCAUUAGCUACA	2323
12099	UGAAGUCGUUCUCAAAAAG	673	12099	UGAAGUCGUUCUCAAAAAG	673	12117	CUUUUUGAGAACGACUUCA	2324
12117	GUUAAAGAAAUCUUUGAAU	674	12117	GUUAAAGAAAUCUUUGAAU	674	12135	AUUCAAAGAUUUCUUUAAC	2325
12135	UGUGGCUAAAUCUGAGUUU	675	12135	UGUGGCUAAAUCUGAGUUU	675	12153	AAACUCAGAUUUAGCCACA	2326
12153	UGACCGUGAUGCUGCCAUG	676	12153	UGACCGUGAUGCUGCCAUG	676	12171	CAUGGCAGCAUCACGGUCA	2327
12171	GCAACGCAAGUUGGAAAAG	677	12171	GCAACGCAAGUUGGAAAAG	677	12189	CUUUUCCAACUUGCGUUGC	2328
12189	GAUGGCAGAUCAGGCUAUG	678	12189	GAUGGCAGAUCAGGCUAUG	678	12207	CAUAGCCUGAUCUGCCAUC	2329
12207	GACCCAAAUGUACAAACAG	679	12207	GACCCAAAUGUACAAACAG	679	12225	CUGUUUGUACAUUUGGGUC	2330
12225	GGCAAGAUCUGAGGACAAG	680	12225	GGCAAGAUCUGAGGACAAG	680	12243	CUUGUCCUCAGAUCUUGCC	2331
12243	GAGGGCAAAAGUAACUAGU	681	12243	GAGGGCAAAAGUAACUAGU	681	12261	ACUAGUUACUUUUGCCCUC	2332
12261	UGCUAUGCAAACAAUGCUC	682	12261	UGCUAUGCAAACAAUGCUC	682	12279	GAGCAUUGUUUGCAUAGCA	2333
12279	CUUCACUAUGCUUAGGAAG	683	12279	CUUCACUAUGCUUAGGAAG	683	12297	CUUCCUAAGCAUAGUGAAG	2334
12297	GCUUGAUAAUGAUGCACUU	684	12297	GCUUGAUAAUGAUGCACUU	684	12315	AAGUGCAUCAUUAUCAAGC	2335
12315	UAACAACAUUAUCAACAAU	685	12315	UAACAACAUUAUCAACAAU	685	12333	AUUGUUGAUAAUGUUGUUA	2336
12333	UGCGCGUGAUGGUUGUGUU	686	12333	UGCGCGUGAUGGUUGUGUU	686	12351	AACACAACCAUCACGCGCA	2337
12351	UCCACUCAACAUCAUACCA	687	12351	UCCACUCAACAUCAUACCA	687	12369	UGGUAUGAUGUUGAGUGGA	2338
12369	AUUGACUACAGCAGCCAAA	688	12369	AUUGACUACAGCAGCCAAA	688	12387	UUUGGCUGCUGUAGUCAAU	2339
12387	ACUCAUGGUUGUUGUCCCU	689	12387	ACUCAUGGUUGUUGUCCCU	689	12405	AGGGACAACAACCAUGAGU	2340
12405	UGAUUAUGGUACCUACAAG	690	12405	UGAUUAUGGUACCUACAAG	690	12423	CUUGUAGGUACCAUAAUCA	2341
12423	GAACACUUGUGAUGGUAAC	691	12423	GAACACUUGUGAUGGUAAC	691	12441	GUUACCAUCACAAGUGUUC	2342
12441	CACCUUUACAUAUGCAUCU	692	12441	CACCUUUACAUAUGCAUCU	692	12459	AGAUGCAUAUGUAAAGGUG	2343
12459	UGCACUCUGGGAAAUCCAG	693	12459	UGCACUCUGGGAAAUCCAG	693	12477	CUGGAUUUCCCAGAGUGCA	2344
12477	GCAAGUUGUUGAUGCGGAU	694	12477	GCAAGUUGUUGAUGCGGAU	694	12495	AUCCGCAUCAACAACUUGC	2345
12495	UAGCAAGAUUGUUCAACUU	695	12495	UAGCAAGAUUGUUCAACUU	695	12513	AAGUUGAACAAUCUUGCUA	2346
12513	UAGUGAAAUUAACAUGGAC	696	12513	UAGUGAAAUUAACAUGGAC	696	12531	GUCCAUGUUAAUUUCACUA	2347
12531	CAAUUCACCAAAUUUGGCU	697	12531	CAAUUCACCAAAUUUGGCU	697	12549	AGCCAAAUUUGGUGAAUUG	2348
12549	UUGGCCUCUUAUUGUUACA	698	12549	UUGGCCUCUUAUUGUUACA	698	12567	UGUAACAAUAAGAGGCCAA	2349
12567	AGCUCUAAGAGCCAACUCA	699	12567	AGCUCUAAGAGCCAACUCA	699	12585	UGAGUUGGCUCUUAGAGCU	2350
12585	AGCUGUUAAACUACAGAAU	700	12585	AGCUGUUAAACUACAGAAU	700	12603	AUUCUGUAGUUUAACAGCU	2351
12603	UAAUGAACUGAGUCCAGUA	701	12603	UAAUGAACUGAGUCCAGUA	701	12621	UACUGGACUCAGUUCAUUA	2352
12621	AGCACUACGACAGAUGUCC	702	12621	AGCACUACGACAGAUGUCC	702	12639	GGACAUCUGUCGUAGUGCU	2353
12639	CUGUGCGGCUGGUACCACA	703	12639	CUGUGCGGCUGGUACCACA	703	12657	UGUGGUACCAGCCGCACAG	2354
12657	ACAAACAGCUUGUACUGAU	704	12657	ACAAACAGCUUGUACUGAU	704	12675	AUCAGUACAAGCUGUUUGU	2355
12675	UGACAAUGCACUUGCCUAC	705	12675	UGACAAUGCACUUGCCUAC	705	12693	GUAGGCAAGUGCAUUGUCA	2356
12693	CUAUAACAAUUCGAAGGGA	706	12693	CUAUAACAAUUCGAAGGGA	706	12711	UCCCUUCGAAUUGUUAUAG	2357
12711	AGGUAGGUUUGUGCUGGCA	707	12711	AGGUAGGUUUGUGCUGGCA	707	12729	UGCCAGCACAAACCUACCU	2358
12729	AUUACUAUCAGACCACCAA	708	12729	AUUACUAUCAGACCACCAA	708	12747	UUGGUGGUCUGAUAGUAAU	2359

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12747	AGAUCUCAAAUGGGCUAGA	709	12747	AGAUCUCAAAUGGGCUAGA	709	12765	UCUAGCCCAUUUGAGAUCU	2360
12765	AUUCCCUAAGAGUGAUGGU	710	12765	AUUCCCUAAGAGUGAUGGU	710	12783	ACCAUCACUCUUAGGGAAU	2361
12783	UACAGGUACAAUUUACACA	711	12783	UACAGGUACAAUUUACACA	711	12801	UGUGUAAAUUGUACCUGUA	2362
12801	AGAACUGGAACCACCUUGU	712	12801	AGAACUGGAACCACCUUGU	712	12819	ACAAGGUGGUUCCAGUUCU	2363
12819	UAGGUUUGUUACAGACACA	713	12819	UAGGUUUGUUACAGACACA	713	12837	UGUGUCUGUAACAAACCUA	2364
12837	ACCAAAAGGGCCUAAAGUG	714	12837	ACCAAAAGGGCCUAAAGUG	714	12855	CACUUUAGGCCCUUUUGGU	2365
12855	GAAAUACUUGUACUUCAUC	715	12855	GAAAUACUUGUACUUCAUC	715	12873	GAUGAAGUACAAGUAUUUC	2366
12873	CAAAGGCUUAAACAACCUA	716	12873	CAAAGGCUUAAACAACCUA	716	12891	UAGGUUGUUUAAGCCUUUG	2367
12891	AAAUAGAGGUAUGGUGCUG	717	12891	AAAUAGAGGUAUGGUGCUG	717	12909	CAGCACCAUACCUCUAUUU	2368
12909	GGGCAGUUUAGCUGCUACA	718	12909	GGGCAGUUUAGCUGCUACA	718	12927	UGUAGCAGCUAAACUGCCC	2369
12927	AGUACGUCUUCAGGCUGGA	719	12927	AGUACGUCUUCAGGCUGGA	719	12945	UCCAGCCUGAAGACGUACU	2370
12945	AAAUGCUACAGAAGUACCU	720	12945	AAAUGCUACAGAAGUACCU	720	12963	AGGUACUUCUGUAGCAUUU	2371
12963	UGCCAAUUCAACUGUGCUU	721	12963	UGCCAAUUCAACUGUGCUU	721	12981	AAGCACAGUUGAAUUGGCA	2372
12981	UUCCUUCUGUGCUUUUGCA	722	12981	UUCCUUCUGUGCUUUUGCA	722	12999	UGCAAAAGCACAGAAGGAA	2373
12999	AGUAGACCCUGCUAAAGCA	723	12999	AGUAGACCCUGCUAAAGCA	723	13017	UGCUUUAGCAGGGUCUACU	2374
13017	AUAUAAGGAUUACCUAGCA	724	13017	AUAUAAGGAUUACCUAGCA	724	13035	UGCUAGGUAAUCCUUAUAU	2375
13035	AAGUGGAGGACAACCAAUC	725	13035	AAGUGGAGGACAACCAAUC	725	13053	GAUUGGUUGUCCUCCACUU	2376
13053	CACCAACUGUGUGAAGAUG	726	13053	CACCAACUGUGUGAAGAUG	726	13071	CAUCUUCACACAGUUGGUG	2377
13071	GUUGUGUACACACACUGGU	727	13071	GUUGUGUACACACACUGGU	727	13089	ACCAGUGUGUGUACACAAC	2378
13089	UACAGGACAGGCAAUUACU	728	13089	UACAGGACAGGCAAUUACU	728	13107	AGUAAUUGCCUGUCCUGUA	2379
13107	UGUAACACCAGAAGCUAAC	729	13107	UGUAACACCAGAAGCUAAC	729	13125	GUUAGCUUCUGGUGUUACA	2380
13125	CAUGGACCAAGAGUCCUUU	730	13125	CAUGGACCAAGAGUCCUUU	730	13143	AAAGGACUCUUGGUCCAUG	2381
13143	UGGUGGUGCUUCAUGUUGU	731	13143	UGGUGGUGCUUCAUGUUGU	731	13161	ACAACAUGAAGCACCACCA	2382
13161	UCUGUAUUGUAGAUGCCAC	732	13161	UCUGUAUUGUAGAUGCCAC	732	13179	GUGGCAUCUACAAUACAGA	2383
13179	CAUUGACCAUCCAAAUCCU	733	13179	CAUUGACCAUCCAAAUCCU	733	13197	AGGAUUUGGAUGGUCAAUG	2384
13197	UAAAGGAUUCUGUGACUUG	734	13197	UAAAGGAUUCUGUGACUUG	734	13215	CAAGUCACAGAAUCCUUUA	2385
13215	GAAAGGUAAGUACGUCCAA	735	13215	GAAAGGUAAGUACGUCCAA	735	13233	UUGGACGUACUUACCUUUC	2386
13233	AAUACCUACCACUUGUGCU	736	13233	AAUACCUACCACUUGUGCU	736	13251	AGCACAAGUGGUAGGUAUU	2387
13251	UAAUGACCCAGUGGGUUUU	737	13251	UAAUGACCCAGUGGGUUUU	737	13269	AAAACCCACUGGGUCAUUA	2388
13269	UACACUUAGAAACACAGUC	738	13269	UACACUUAGAAACACAGUC	738	13287	GACUGUGUUUCUAAGUGUA	2389
13287	CUGUACCGUCUGCGGAAUG	739	13287	CUGUACCGUCUGCGGAAUG	739	13305	CAUUCCGCAGACGGUACAG	2390
13305	GUGGAAAGGUUAUGGCUGU	740	13305	GUGGAAAGGUUAUGGCUGU	740	13323	ACAGCCAUAACCUUUCCAC	2391
13323	UAGUUGUGACCAACUCCGC	741	13323	UAGUUGUGACCAACUCCGC	741	13341	GCGGAGUUGGUCACAACUA	2392
13341	CGAACCCUUGAUGCAGUCU	742	13341	CGAACCCUUGAUGCAGUCU	742	13359	AGACUGCAUCAAGGGUUCG	2393
13359	UGCGGAUGCAUCAACGUUU	743	13359	UGCGGAUGCAUCAACGUUU	743	13377	AAACGUUGAUGCAUCCGCA	2394
13377	UUUAAACGGGUUUGCGGUG	744	13377	UUUAAACGGGUUUGCGGUG	744	13395	CACCGCAAACCCGUUUAAA	2395
13395	GUAAGUGCAGCCCGUCUUA	745	13395	GUAAGUGCAGCCCGUCUUA	745	13413	UAAGACGGGCUGCACUUAC	2396
13413	ACACCGUGCGGCACAGGCA	746	13413	ACACCGUGCGGCACAGGCA	746	13431	UGCCUGUGCCGCACGGUGU	2397
13431	ACUAGUACUGAUGUCGUCU	747	13431	ACUAGUACUGAUGUCGUCU	747	13449	AGACGACAUCAGUACUAGU	2398
13449	UACAGGGCUUUUGAUAUUU	748	13449	UACAGGGCUUUUGAUAUUU	748	13467	AAAUAUCAAAAGCCCUGUA	2399
13467	UACAACGAAAAAGUUGCUG	749	13467	UACAACGAAAAAGUUGCUG	749	13485	CAGCAACUUUUUCGUUGUA	2400
13485	GGUUUUGCAAAGUUCCUAA	750	13485	GGUUUUGCAAAGUUCCUAA	750	13503	UUAGGAACUUUGCAAAACC	2401

13503	AAAACUAAUUGCUGUCGCU	751	13503	AAAACUAAUUGCUGUCGCU	751	13521	AGCGACAGCAAUUAGUUUU	2402
13521	UUCCAGGAGAAGGAUGAGG	752	13521	UUCCAGGAGAAGGAUGAGG	752	13539	CCUCAUCCUUCUCCUGGAA	2403
13539	GAAGGCAAUUUAUUAGACU	753	13539	GAAGGCAAUUUAUUAGACU	753	13557	AGUCUAAUAAAUUGCCUUC	2404
13557	UCUUACUUUGUAGUUAAGA	754	13557	UCUUACUUUGUAGUUAAGA	754	13575	UCUUAACUACAAAGUAAGA	2405
13575	AGGCAUACUAUGUCUAACU	755	13575	AGGCAUACUAUGUCUAACU	755	13593	AGUUAGACAUAGUAUGCCU	2406
13593	UACCAACAUGAAGAGACUA	756	13593	UACCAACAUGAAGAGACUA	756	13611	UAGUCUCUUCAUGUUGGUA	2407
13611	AUUUAUAACUUGGUUAAAG	757	13611	AUUUAUAACUUGGUUAAAG	757	13629	CUUUAACCAAGUUAUAAAU	2408
13629	GAUUGUCCAGCGGUUGCUG	758	13629	GAUUGUCCAGCGGUUGCUG	758	13647	CAGCAACCGCUGGACAAUC	2409
13647	GUCCAUGACUUUUUCAAGU	759	13647	GUCCAUGACUUUUUCAAGU	759	13665	ACUUGAAAAAGUCAUGGAC	2410
13665	UUUAGAGUAGAUGGUGACA	760	13665	UUUAGAGUAGAUGGUGACA	760	13683	UGUCACCAUCUACUCUAAA	2411
13683	AUGGUACCACAUAUAUCAC	761	13683	AUGGUACCACAUAUAUCAC	761	13701	GUGAUAUAUGUGGUACCAU	2412
13701	CGUCAGCGUCUAACUAAAU	762	13701	CGUCAGCGUCUAACUAAAU	762	13719	AUUUAGUUAGACGCUGACG	2413
13719	UACACAAUGGCUGAUUUAG	763	13719	UACACAAUGGCUGAUUUAG	763	13737	CUAAAUCAGCCAUUGUGUA	2414
13737	GUCUAUGCUCUACGUCAUU	764	13737	GUCUAUGCUCUACGUCAUU	764	13755	AAUGACGUAGAGCAUAGAC	2415
13755	UUUGAUGAGGGUAAUUGUG	765	13755	UUUGAUGAGGGUAAUUGUG	765	13773	CACAAUUACCCUCAUCAAA	2416
13773	GAUACAUUAAAAGAAAUAC	766	13773	GAUACAUUAAAAGAAAUAC	766	13791	GUAUUUCUUUUAAUGUAUC	2417
13791	CUCGUCACAUACAAUUGCU	767	13791	CUCGUCACAUACAAUUGCU	767	13809	AGCAAUUGUAUGUGACGAG	2418
13809	UGUGAUGAUGAUUAUUUCA	768	13809	UGUGAUGAUGAUUAUUUCA	768	13827	UGAAAUAAUCAUCAUCACA	2419
13827	AAUAAGAAGGAUUGGUAUG	769	13827	AAUAAGAAGGAUUGGUAUG	769	13845	CAUACCAAUCCUUCUUAUU	2420
13845	GACUUCGUAGAGAAUCCUG	770	13845	GACUUCGUAGAGAAUCCUG	770	13863	CAGGAUUCUCUACGAAGUC	2421
13863	GACAUCUUACGCGUAUAUG	771	13863	GACAUCUUACGCGUAUAUG	771	13881	CAUAUACGCGUAAGAUGUC	2422
13881	GCUAACUUAGGUGAGCGUG	772	13881	GCUAACUUAGGUGAGCGUG	772	13899	CACGCUCACCUAAGUUAGC	2423
13899	GUACGCCAAUCAUUAUUAA	773	13899	GUACGCCAAUCAUUAUUAA	773	13917	UUAAUAAUGAUUGGCGUAC	2424
13917	AAGACUGUACAAUUCUGCG	774	13917	AAGACUGUACAAUUCUGCG	774	13935	CGCAGAAUUGUACAGUCUU	2425
13935	GAUGCUAUGCGUGAUGCAG	775	13935	GAUGCUAUGCGUGAUGCAG	775	13953	CUGCAUCACGCAUAGCAUC	2426
13953	GGCAUUGUAGGCGUACUGA	776	13953	GGCAUUGUAGGCGUACUGA	776	13971	UCAGUACGCCUACAAUGCC	2427
13971	ACAUUAGAUAAUCAGGAUC	777	13971	ACAUUAGAUAAUCAGGAUC	777	13989	GAUCCUGAUUAUCUAAUGU	2428
13989	CUUAAUGGGAACUGGUACG	778	13989	CUUAAUGGGAACUGGUACG	778	14007	CGUACCAGUUCCCAUUAAG	2429
14007	GAUUUCGGUGAUUUCGUAC	779	14007	GAUUUCGGUGAUUUCGUAC	779	14025	GUACGAAAUCACCGAAAUC	2430
14025	CAAGUAGCACCAGGCUGCG	780	14025	CAAGUAGCACCAGGCUGCG	780	14043	CGCAGCCUGGUGCUACUUG	2431
14043	GGAGUUCCUAUUGUGGAUU	781	14043	GGAGUUCCUAUUGUGGAUU	781	14061	AAUCCACAAUAGGAACUCC	2432
14061	UCAUAUUACUCAUUGCUGA	782	14061	UCAUAUUACUCAUUGCUGA	782	14079	UCAGCAAUGAGUAAUAUGA	2433
14079	AUGCCCAUCCUCACUUUGA	783	14079	AUGCCCAUCCUCACUUUGA	783	14097	UCAAAGUGAGGAUGGGCAU	2434
14097	ACUAGGGCAUUGGCUGCUG	784	14097	ACUAGGGCAUUGGCUGCUG	784	14115	CAGCAGCCAAUGCCCUAGU	2435
14115	GAGUCCCAUAUGGAUGCUG	785	14115	GAGUCCCAUAUGGAUGCUG	785	14133	CAGCAUCCAUAUGGGACUC	2436
14133	GAUCUCGCAAAACCACUUA	786	14133	GAUCUCGCAAAACCACUUA	786	14151	UAAGUGGUUUUGCGAGAUC	2437
14151	AUUAAGUGGGAUUUGCUGA	787	14151	AUUAAGUGGGAUUUGCUGA	787	14169	UCAGCAAAUCCCACUUAAU	2438
14169	AAAUAUGAUUUUACGGAAG	788	14169	AAAUAUGAUUUUACGGAAG	788	14187	CUUCCGUAAAAUCAUAUUU	2439
14187	GAGAGACUUUGUCUCUUCG	789	14187	GAGAGACUUUGUCUCUUCG	789	14205	CGAAGAGACAAAGUCUCUC	2440
14205	GACCGUUAUUUUAAAUAUU	790	14205	GACCGUUAUUUUAAAUAUU	790	14223	AAUAUUUAAAAUAACGGUC	2441
14223	UGGGACCAGACAUACCAUC	791	14223	UGGGACCAGACAUACCAUC	791	14241	GAUGGUAUGUCUGGUCCCA	2442
14241	CCCAAUUGUAUUAACUGUU	792	14241	CCCAAUUGUAUUAACUGUU	792	14259	AACAGUUAAUACAAUUGGG	2443

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14259	UUGGAUGAUAGGUGUAUCC	793	14259	UUGGAUGAUAGGUGUAUCC	793	14277	GGAUACACCUAUCAUCCAA	2444
14277	CUUCAUUGUGCAAACUUUA	794	14277	CUUCAUUGUGCAAACUUUA	794	14295	UAAAGUUUGCACAAUGAAG	2445
14295	AAUGUGUUAUUUUCUACUG	795	14295	AAUGUGUUAUUUUCUACUG	795	14313	CAGUAGAAAAUAACACAUU	2446
14313	GUGUUUCCACCUACAAGUU	796	14313	GUGUUUCCACCUACAAGUU	796	14331	AACUUGUAGGUGGAAACAC	2447
14331	UUUGGACCACUAGUAAGAA	797	14331	UUUGGACCACUAGUAAGAA	797	14349	UUCUUACUAGUGGUCCAAA	2448
14349	AAAAUAUUUGUAGAUGGUG	798	14349	AAAAUAUUUGUAGAUGGUG	798	14367	CACCAUCUACAAAUAUUUU	2449
14367	GUUCCUUUUGUUGUUUCAA	799	14367	GUUCCUUUUGUUGUUUCAA	799	14385	UUGAAACAACAAAAGGAAC	2450
14385	ACUGGAUACCAUUUUCGUG	800	14385	ACUGGAUACCAUUUUCGUG	800	14403	CACGAAAAUGGUAUCCAGU	2451
14403	GAGUUAGGAGUCGUACAUA	801	14403	GAGUUAGGAGUCGUACAUA	801	14421	UAUGUACGACUCCUAACUC	2452
14421	AAUCAGGAUGUAAACUUAC	802	14421	AAUCAGGAUGUAAACUUAC	802	14439	GUAAGUUUACAUCCUGAUU	2453
14439	CAUAGCUCGCGUCUCAGUU	803	14439	CAUAGCUCGCGUCUCAGUU	803	14457	AACUGAGACGCGAGCUAUG	2454
14457	UUCAAGGAACUUUUAGUGU	804	14457	UUCAAGGAACUUUUAGUGU	804	14475	ACACUAAAAGUUCCUUGAA	2455
14475	UAUGCUGCUGAUCCAGCUA	805	14475	UAUGCUGCUGAUCCAGCUA	805	14493	UAGCUGGAUCAGCAGCAUA	2456
14493	AUGCAUGCAGCUUCUGGCA	806	14493	AUGCAUGCAGCUUCUGGCA	806	14511	UGCCAGAAGCUGCAUGCAU	2457
14511	AAUUUAUUGCUAGAUAAAC	807	14511	AAUUUAUUGCUAGAUAAAC	807	14529	GUUUAUCUAGCAAUAAAUU	2458
14529	CGCACUACAUGCUUUUCAG	808	14529	CGCACUACAUGCUUUUCAG	808	14547	CUGAAAAGCAUGUAGUGCG	2459
14547	GUAGCUGCACUAACAAACA	809	14547	GUAGCUGCACUAACAAACA	809	14565	UGUUUGUUAGUGCAGCUAC	2460
14565	AAUGUUGCUUUUCAAACUG	810	14565	AAUGUUGCUUUUCAAACUG	810	14583	CAGUUUGAAAAGCAACAUU	2461
14583	GUCAAACCCGGUAAUUUUA	811	14583	GUCAAACCCGGUAAUUUUA	811	14601	UAAAAUUACCGGGUUUGAC	2462
14601	AAUAAAGACUUUUAUGACU	812	14601	AAUAAAGACUUUUAUGACU	812	14619	AGUCAUAAAAGUCUUUAUU	2463
14619	UUUGCUGUGUCUAAAGGUU	813	14619	UUUGCUGUGUCUAAAGGUU	813	14637	AACCUUUAGACACAGCAAA	2464
14637	UUCUUUAAGGAAGGAAGUU	814	14637	UUCUUUAAGGAAGGAAGUU	814	14655	AACUUCCUUCCUUAAAGAA	2465
14655	UCUGUUGAACUAAAACACU	815	14655	UCUGUUGAACUAAAACACU	815	14673	AGUGUUUUAGUUCAACAGA	2466
14673	UUCUUCUUUGCUCAGGAUG	816	14673	UUCUUCUUUGCUCAGGAUG	816	14691	CAUCCUGAGCAAAGAAGAA	2467
14691	GGCAACGCUGCUAUCAGUG	817	14691	GGCAACGCUGCUAUCAGUG	817	14709	CACUGAUAGCAGCGUUGCC	2468
14709	GAUUAUGACUAUUAUCGUU	818	14709	GAUUAUGACUAUUAUCGUU	818	14727	AACGAUAAUAGUCAUAAUC	2469
14727	UAUAAUCUGCCAACAAUGU	819	14727	UAUAAUCUGCCAACAAUGU	819	14745	ACAUUGUUGGCAGAUUAUA	2470
14745	UGUGAUAUCAGACAACUCC	820	14745	UGUGAUAUCAGACAACUCC	820	14763	GGAGUUGUCUGAUAUCACA	2471
14763	CUAUUCGUAGUUGAAGUUG	821	14763	CUAUUCGUAGUUGAAGUUG	821	14781	CAACUUCAACUACGAAUAG	2472
14781	GUUGAUAAAUACUUUGAUU	822	14781	GUUGAUAAAUACUUUGAUU	822	14799	AAUCAAAGUAUUUAUCAAC	2473
14799	UGUUACGAUGGUGGCUGUA	823	14799	UGUUACGAUGGUGGCUGUA	823	14817	UACAGCCACCAUCGUAACA	2474
14817	AUUAAUGCCAACCAAGUAA	824	14817	AUUAAUGCCAACCAAGUAA	824	14835	UUACUUGGUUGGCAUUAAU	2475
14835	AUCGUUAACAAUCUGGAUA	825	14835	AUCGUUAACAAUCUGGAUA	825	14853	UAUCCAGAUUGUUAACGAU	2476
14853	AAAUCAGCUGGUUUCCCAU	826	14853	AAAUCAGCUGGUUUCCCAU	826	14871	AUGGGAAACCAGCUGAUUU	2477
14871	UUUAAUAAAUGGGGUAAGG	827	14871	UUUAAUAAAUGGGGUAAGG	827	14889	CCUUACCCCAUUUAUUAAA	2478
14889	GCUAGACUUUAUUAUGACU	828	14889	GCUAGACUUUAUUAUGACU	828	14907	AGUCAUAAUAAAGUCUAGC	2479
14907	UCAAUGAGUUAUGAGGAUC	829	14907	UCAAUGAGUUAUGAGGAUC	829	14925	GAUCCUCAUAACUCAUUGA	2480
14925	CAAGAUGCACUUUUCGCGU	830	14925	CAAGAUGCACUUUUCGCGU	830	14943	ACGCGAAAAGUGCAUCUUG	2481
14943	UAUACUAAGCGUAAUGUCA	831	14943	UAUACUAAGCGUAAUGUCA	831	14961	UGACAUUACGCUUAGUAUA	2482
14961	AUCCCUACUAUAACUCAAA	832	14961	AUCCCUACUAUAACUCAAA	832	14979	UUUGAGUUAUAGUAGGGAU	2483
14979	AUGAAUCUUAAGUAUGCCA	833	14979	AUGAAUCUUAAGUAUGCCA	833	14997	UGGCAUACUUAAGAUUCAU	2484
14997	AUUAGUGCAAAGAAUAGAG	834	14997	AUUAGUGCAAAGAAUAGAG	834	15015	CUCUAUUCUUUGCACUAAU	2485

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15015	GCUCGCACCGUAGCUGGUG	835	15015	GCUCGCACCGUAGCUGGUG	835	15033	CACCAGCUACGGUGCGAGC	2486
15033	GUCUCUAUCUGUAGUACUA	836	15033	GUCUCUAUCUGUAGUACUA	836	15051	UAGUACUACAGAUAGAGAC	2487
15051	AUGACAAAUAGACAGUUUC	837	15051	AUGACAAAUAGACAGUUUC	837	15069	GAAACUGUCUAUUUGUCAU	2488
15069	CAUCAGAAAUUAUUGAAGU	838	15069	CAUCAGAAAUUAUUGAAGU	838	15087	ACUUCAAUAAUUUCUGAUG	2489
15087	UCAAUAGCCGCCACUAGAG	839	15087	UCAAUAGCCGCCACUAGAG	839	15105	CUCUAGUGGCGGCUAUUGA	2490
15105	GGAGCUACUGUGGUAAUUG	840	15105	GGAGCUACUGUGGUAAUUG	840	15123	CAAUUACCACAGUAGCUCC	2491
15123	GGAACAAGCAAGUUUUACG	841	15123	GGAACAAGCAAGUUUUACG	841	15141	CGUAAAACUUGCUUGUUCC	2492
15141	GGUGGCUGGCAUAAUAUGU	842	15141	GGUGGCUGGCAUAAUAUGU	842	15159	ACAUAUUAUGCCAGCCACC	2493
15159	UUAAAAACUGUUUACAGUG	843	15159	UUAAAAACUGUUUACAGUG	843	15177	CACUGUAAACAGUUUUUAA	2494
15177	GAUGUAGAAACUCCACACC	844	15177	GAUGUAGAAACUCCACACC	844	15195	GGUGUGGAGUUUCUACAUC	2495
15195	CUUAUGGGUUGGGAUUAUC	845	15195	CUUAUGGGUUGGGAUUAUC	845	15213	GAUAAUCCCAACCCAUAAG	2496
15213	CCAAAAUGUGACAGAGCCA	846	15213	CCAAAAUGUGACAGAGCCA	846	15231	UGGCUCUGUCACAUUUUGG	2497
15231	AUGCCUAACAUGCUUAGGA	847	15231	AUGCCUAACAUGCUUAGGA	847	15249	UCCUAAGCAUGUUAGGCAU	2498
15249	AUAAUGGCCUCUCUUGUUC	848	15249	AUAAUGGCCUCUCUUGUUC	848	15267	GAACAAGAGAGGCCAUUAU	2499
15267	CUUGCUCGCAAACAUAACA	849	15267	CUUGCUCGCAAACAUAACA	849	15285	UGUUAUGUUUGCGAGCAAG	2500
15285	ACUUGCUGUAACUUAUCAC	850	15285	ACUUGCUGUAACUUAUCAC	850	15303	GUGAUAAGUUACAGCAAGU	2501
15303	CACCGUUUCUACAGGUUAG	851	15303	CACCGUUUCUACAGGUUAG	851	15321	CUAACCUGUAGAAACGGUG	2502
15321	GCUAACGAGUGUGCGCAAG	852	15321	GCUAACGAGUGUGCGCAAG	852	15339	CUUGCGCACACUCGUUAGC	2503
15339	GUAUUAAGUGAGAUGGUCA	853	15339	GUAUUAAGUGAGAUGGUCA	853	15357	UGACCAUCUCACUUAAUAC	2504
15357	AUGUGUGGCGGCUCACUAU	854	15357	AUGUGUGGCGGCUCACUAU	854	15375	AUAGUGAGCCGCCACACAU	2505
15375	UAUGUUAAACCAGGUGGAA	855	15375	UAUGUUAAACCAGGUGGAA	855	15393	UUCCACCUGGUUUAACAUA	2506
15393	ACAUCAUCCGGUGAUGCUA	856	15393	ACAUCAUCCGGUGAUGCUA	856	15411	UAGCAUCACCGGAUGAUGU	2507
15411	ACAACUGCUUAUGCUAAUA	857	15411	ACAACUGCUUAUGCUAAUA	857	15429	UAUUAGCAUAAGCAGUUGU	2508
15429	AGUGUCUUUAACAUUUGUC	858	15429	AGUGUCUUUAACAUUUGUC	858	15447	GACAAAUGUUAAAGACACU	2509
15447	CAAGCUGUUACAGCCAAUG	859	15447	CAAGCUGUUACAGCCAAUG	859	15465	CAUUGGCUGUAACAGCUUG	2510
15465	GUAAAUGCACUUCUUUCAA	860	15465	GUAAAUGCACUUCUUUCAA	860	15483	UUGAAAGAAGUGCAUUUAC	2511
15483	ACUGAUGGUAAUAAGAUAG	861	15483	ACUGAUGGUAAUAAGAUAG	861	15501	CUAUCUUAUUACCAUCAGU	2512
15501	GCUGACAAGUAUGUCCGCA	862	15501	GCUGACAAGUAUGUCCGCA	862	15519	UGCGGACAUACUUGUCAGC	2513
15519	AAUCUACAACACAGGCUCU	863	15519	AAUCUACAACACAGGCUCU	863	15537	AGAGCCUGUGUUGUAGAUU	2514
15537	UAUGAGUGUCUCUAUAGAA	864	15537	UAUGAGUGUCUCUAUAGAA	864	15555	UUCUAUAGAGACACUCAUA	2515
15555	AAUAGGGAUGUUGAUCAUG	865	15555	AAUAGGGAUGUUGAUCAUG	865	15573	CAUGAUCAACAUCCCUAUU	2516
15573	GAAUUCGUGGAUGAGUUUU	866	15573	GAAUUCGUGGAUGAGUUUU	866	15591	AAAACUCAUCCACGAAUUC	2517
15591	UACGCUUACCUGCGUAAAC	867	15591	UACGCUUACCUGCGUAAAC	867	15609	GUUUACGCAGGUAAGCGUA	2518
15609	CAUUUCUCCAUGAUGAUUC	868	15609	CAUUUCUCCAUGAUGAUUC	868	15627	GAAUCAUCAUGGAGAAAUG	2519
15627	CUUUCUGAUGAUGCCGUUG	869	15627	CUUUCUGAUGAUGCCGUUG	869	15645	CAACGGCAUCAUCAGAAAG	2520
15645	GUGUGCUAUAACAGUAACU	870	15645	GUGUGCUAUAACAGUAACU	870	15663	AGUUACUGUUAUAGCACAC	2521
15663	UAUGCGGCUCAAGGUUUAG	871	15663	UAUGCGGCUCAAGGUUUAG	871	15681	CUAAACCUUGAGCCGCAUA	2522
15681	GUAGCUAGCAUUAAGAACU	872	15681	GUAGCUAGCAUUAAGAACU	872	15699	AGUUCUUAAUGCUAGCUAC	2523
15699	UUUAAGGCAGUUCUUUAUU	873	15699	UUUAAGGCAGUUCUUUAUU	873	15717	AAUAAAGAACUGCCUUAAA	2524
15717	UAUCAAAAUAAUGUGUUCA	874	15717	UAUCAAAAUAAUGUGUUCA	874	15735	UGAACACAUUAUUUUGAUA	2525
15735	AUGUCUGAGGCAAAAUGUU	875	15735	AUGUCUGAGGCAAAAUGUU	875	15753	AACAUUUUGCCUCAGACAU	2526
15753	UGGACUGAGACUGACCUUA	876	15753	UGGACUGAGACUGACCUUA	876	15771	UAAGGUCAGUCUCAGUCCA	2527

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15771	ACUAAAGGACCUCACGAAU	877	15771	ACUAAAGGACCUCACGAAU	877	15789	AUUCGUGAGGUCCUUUAGU	2528
15789	UUUUGCUCACAGCAUACAA	878	15789	UUUUGCUCACAGCAUACAA	878	15807	UUGUAUGCUGUGAGCAAAA	2529
15807	AUGCUAGUUAAACAAGGAG	879	15807	AUGCUAGUUAAACAAGGAG	879	15825	CUCCUUGUUUAACUAGCAU	2530
15825	GAUGAUUACGUGUACCUGC	880	15825	GAUGAUUACGUGUACCUGC	880	15843	GCAGGUACACGUAAUCAUC	2531
15843	CCUUACCCAGAUCCAUCAA	881	15843	CCUUACCCAGAUCCAUCAA	881	15861	UUGAUGGAUCUGGGUAAGG	2532
15861	AGAAUAUUAGGCGCAGGCU	882	15861	AGAAUAUUAGGCGCAGGCU	882	15879	AGCCUGCGCCUAAUAUUCU	2533
15879	UGUUUUGUCGAUGAUAUUG	883	15879	UGUUUUGUCGAUGAUAUUG	883	15897	CAAUAUCAUCGACAAAACA	2534
15897	GUCAAAACAGAUGGUACAC	884	15897	GUCAAAACAGAUGGUACAC	884	15915	GUGUACCAUCUGUUUUGAC	2535
15915	CUUAUGAUUGAAAGGUUCG	885	15915	CUUAUGAUUGAAAGGUUCG	885	15933	CGAACCUUUCAAUCAUAAG	2536
15933	GUGUCACUGGCUAUUGAUG	886	15933	GUGUCACUGGCUAUUGAUG	886	15951	CAUCAAUAGCCAGUGACAC	2537
15951	GCUUACCCACUUACAAAAC	887	15951	GCUUACCCACUUACAAAAC	887	15969	GUUUUGUAAGUGGGUAAGC	2538
15969	CAUCCUAAUCAGGAGUAUG	888	15969	CAUCCUAAUCAGGAGUAUG	888	15987	CAUACUCCUGAUUAGGAUG	2539
15987	GCUGAUGUCUUUCACUUGU	889	15987	GCUGAUGUCUUUCACUUGU	889	16005	ACAAGUGAAAGACAUCAGC	2540
16005	UAUUUACAAUACAUUAGAA	890	16005	UAUUUACAAUACAUUAGAA	890	16023	UUCUAAUGUAUUGUAAAUA	2541
16023	AAGUUACAUGAUGAGCUUA	891	16023	AAGUUACAUGAUGAGCUUA	891	16041	UAAGCUCAUCAUGUAACUU	2542
16041	ACUGGCCACAUGUUGGACA	892	16041	ACUGGCCACAUGUUGGACA	892	16059	UGUCCAACAUGUGGCCAGU	2543
16059	AUGUAUUCCGUAAUGCUAA	893	16059	AUGUAUUCCGUAAUGCUAA	893	16077	UUAGCAUUACGGAAUACAU	2544
16077	ACUAAUGAUAACACCUCAC	894	16077	ACUAAUGAUAACACCUCAC	894	16095	GUGAGGUGUUAUCAUUAGU	2545
16095	CGGUACUGGGAACCUGAGU	895	16095	CGGUACUGGGAACCUGAGU	895	16113	ACUCAGGUUCCCAGUACCG	2546
16113	UUUUAUGAGGCUAUGUACA	896	16113	UUUUAUGAGGCUAUGUACA	896	16131	UGUACAUAGCCUCAUAAAA	2547
16131	ACACCACAUACAGUCUUGC	897	16131	ACACCACAUACAGUCUUGC	897	16149	GCAAGACUGUAUGUGGUGU	2548
16149	CAGGCUGUAGGUGCUUGUG	898	16149	CAGGCUGUAGGUGCUUGUG	898	16167	CACAAGCACCUACAGCCUG	2549
16167	GUAUUGUGCAAUUCACAGA	899	16167	GUAUUGUGCAAUUCACAGA	899	16185	UCUGUGAAUUGCACAAUAC	2550
16185	ACUUCACUUCGUUGCGGUG	900	16185	ACUUCACUUCGUUGCGGUG	900	16203	CACCGCAACGAAGUGAAGU	2551
16203	GCCUGUAUUAGGAGACCAU	901	16203	GCCUGUAUUAGGAGACCAU	901	16221	AUGGUCUCCUAAUACAGGC	2552
16221	UUCCUAUGUUGCAAGUGCU	902	16221	UUCCUAUGUUGCAAGUGCU	902	16239	AGCACUUGCAACAUAGGAA	2553
16239	UGCUAUGACCAUGUCAUUU	903	16239	UGCUAUGACCAUGUCAUUU	903	16257	AAAUGACAUGGUCAUAGCA	2554
16257	UCAACAUCACACAAAUUAG	904	16257	UCAACAUCACACAAAUUAG	904	16275	CUAAUUUGUGUGAUGUUGA	2555
16275	GUGUUGUCUGUUAAUCCCU	905	16275	GUGUUGUCUGUUAAUCCCU	905	16293	AGGGAUUAACAGACAACAC	2556
16293	UAUGUUUGCAAUGCCCCAG	906	16293	UAUGUUUGCAAUGCCCCAG	906	16311	CUGGGGCAUUGCAAACAUA	2557
16311	GGUUGUGAUGUCACUGAUG	907	16311	GGUUGUGAUGUCACUGAUG	907	16329	CAUCAGUGACAUCACAACC	2558
16329	GUGACACAACUGUAUCUAG	908	16329	GUGACACAACUGUAUCUAG	908	16347	CUAGAUACAGUUGUGUCAC	2559
16347	GGAGGUAUGAGCUAUUAUU	909	16347	GGAGGUAUGAGCUAUUAUU	909	16365	AAUAAUAGCUCAUACCUCC	2560
16365	UGCAAGUCACAUAAGCCUC	910	16365	UGCAAGUCACAUAAGCCUC	910	16383	GAGGCUUAUGUGACUUGCA	2561
16383	CCCAUUAGUUUUCCAUUAU	911	16383	CCCAUUAGUUUUCCAUUAU	911	16401	AUAAUGGAAAACUAAUGGG	2562
16401	UGUGCUAAUGGUCAGGUUU	912	16401	UGUGCUAAUGGUCAGGUUU	912	16419	AAACCUGACCAUUAGCACA	2563
16419	UUUGGUUUAUACAAAAACA	913	16419	UUUGGUUUAUACAAAAACA	913	16437	UGUUUUUGUAUAAACCAAA	2564
16437	ACAUGUGUAGGCAGUGACA	914	16437	ACAUGUGUAGGCAGUGACA	914	16455	UGUCACUGCCUACACAUGU	2565
16455	AAUGUCACUGACUUCAAUG	915	16455	AAUGUCACUGACUUCAAUG	915	16473	CAUUGAAGUCAGUGACAUU	2566
16473	GCGAUAGCAACAUGUGAUU	916	16473	GCGAUAGCAACAUGUGAUU	916	16491	AAUCACAUGUUGCUAUCGC	2567
16491	UGGACUAAUGCUGGCGAUU	917	16491	UGGACUAAUGCUGGCGAUU	917	16509	AAUCGCCAGCAUUAGUCCA	2568
16509	UACAUACUUGCCAACACUU	918	16509	UACAUACUUGCCAACACUU	918	16527	AAGUGUUGGCAAGUAUGUA	2569

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16527	UGUACUGAGAGACUCAAGC	919	16527	UGUACUGAGAGACUCAAGC	919	16545	GCUUGAGUCUCUCAGUACA	2570
16545	CUUUUCGCAGCAGAAACGC	920	16545	CUUUUCGCAGCAGAAACGC	920	16563	GCGUUUCUGCUGCGAAAAG	2571
16563	CUCAAAGCCACUGAGGAAA	921	16563	CUCAAAGCCACUGAGGAAA	921	16581	UUUCCUCAGUGGCUUUGAG	2572
16581	ACAUUUAAGCUGUCAUAUG	922	16581	ACAUUUAAGCUGUCAUAUG	922	16599	CAUAUGACAGCUUAAAUGU	2573
16599	GGUAUUGCCACUGUACGCG	923	16599	GGUAUUGCCACUGUACGCG	923	16617	CGCGUACAGUGGCAAUACC	2574
16617	GAAGUACUCUCUGACAGAG	924	16617	GAAGUACUCUCUGACAGAG	924	16635	CUCUGUCAGAGAGUACUUC	2575
16635	GAAUUGCAUCUUUCAUGGG	925	16635	GAAUUGCAUCUUUCAUGGG	925	16653	CCCAUGAAAGAUGCAAUUC	2576
16653	GAGGUUGGAAAACCUAGAC	926	16653	GAGGUUGGAAAACCUAGAC	926	16671	GUCUAGGUUUUCCAACCUC	2577
16671	CCACCAUUGAACAGAAACU	927	16671	CCACCAUUGAACAGAAACU	927	16689	AGUUUCUGUUCAAUGGUGG	2578
16689	UAUGUCUUUACUGGUUACC	928	16689	UAUGUCUUUACUGGUUACC	928	16707	GGUAACCAGUAAAGACAUA	2579
16707	CGUGUAACUAAAAAUAGUA	929	16707	CGUGUAACUAAAAAUAGUA	929	16725	UACUAUUUUUAGUUACACG	2580
16725	AAAGUACAGAUUGGAGAGU	930	16725	AAAGUACAGAUUGGAGAGU	930	16743	ACUCUCCAAUCUGUACUUU	2581
16743	UACACCUUUGAAAAAGGUG	931	16743	UACACCUUUGAAAAAGGUG	931	16761	CACCUUUUUCAAAGGUGUA	2582
16761	GACUAUGGUGAUGCUGUUG	932	16761	GACUAUGGUGAUGCUGUUG	932	16779	CAACAGCAUCACCAUAGUC	2583
16779	GUGUACAGAGGUACUACGA	933	16779	GUGUACAGAGGUACUACGA	933	16797	UCGUAGUACCUCUGUACAC	2584
16797	ACAUACAAGUUGAAUGUUG	934	16797	ACAUACAAGUUGAAUGUUG	934	16815	CAACAUUCAACUUGUAUGU	2585
16815	GGUGAUUACUUUGUGUUGA	935	16815	GGUGAUUACUUUGUGUUGA	935	16833	UCAACACAAAGUAAUCACC	2586
16833	ACAUCUCACACUGUAAUGC	936	16833	ACAUCUCACACUGUAAUGC	936	16851	GCAUUACAGUGUGAGAUGU	2587
16851	CCACUUAGUGCACCUACUC	937	16851	CCACUUAGUGCACCUACUC	937	16869	GAGUAGGUGCACUAAGUGG	2588
16869	CUAGUGCCACAAGAGCACU	938	16869	CUAGUGCCACAAGAGCACU	938	16887	AGUGCUCUUGUGGCACUAG	2589
16887	UAUGUGAGAAUUACUGGCU	939	16887	UAUGUGAGAAUUACUGGCU	939	16905	AGCCAGUAAUUCUCACAUA	2590
16905	UUGUACCCAACACUCAACA	940	16905	UUGUACCCAACACUCAACA	940	16923	UGUUGAGUGUUGGGUACAA	2591
16923	AUCUCAGAUGAGUUUUCUA	941	16923	AUCUCAGAUGAGUUUUCUA	941	16941	UAGAAAACUCAUCUGAGAU	2592
16941	AGCAAUGUUGCAAAUUAUC	942	16941	AGCAAUGUUGCAAAUUAUC	942	16959	GAUAAUUUGCAACAUUGCU	2593
16959	CAAAAGGUCGGCAUGCAAA	943	16959	CAAAAGGUCGGCAUGCAAA	943	16977	UUUGCAUGCCGACCUUUUG	2594
16977	AAGUACUCUACACUCCAAG	944	16977	AAGUACUCUACACUCCAAG	944	16995	CUUGGAGUGUAGAGUACUU	2595
16995	GGACCACCUGGUACUGGUA	945	16995	GGACCACCUGGUACUGGUA	945	17013	UACCAGUACCAGGUGGUCC	2596
17013	AAGAGUCAUUUUGCCAUCG	946	17013	AAGAGUCAUUUUGCCAUCG	946	17031	CGAUGGCAAAAUGACUCUU	2597
17031	GGACUUGCUCUCUAUUACC	947	17031	GGACUUGCUCUCUAUUACC	947	17049	GGUAAUAGAGAGCAAGUCC	2598
17049	CCAUCUGCUCGCAUAGUGU	948	17049	CCAUCUGCUCGCAUAGUGU	948	17067	ACACUAUGCGAGCAGAUGG	2599
17067	UAUACGGCAUGCUCUCAUG	949	17067	UAUACGGCAUGCUCUCAUG	949	17085	CAUGAGAGCAUGCCGUAUA	2600
17085	GCAGCUGUUGAUGCCCUAU	950	17085	GCAGCUGUUGAUGCCCUAU	950	17103	AUAGGGCAUCAACAGCUGC	2601
17103	UGUGAAAAGGCAUUAAAAU	951	17103	UGUGAAAAGGCAUUAAAAU	951	17121	AUUUUAAUGCCUUUUCACA	2602
17121	UAUUUGCCCAUAGAUAAAU	952	17121	UAUUUGCCCAUAGAUAAAU	952	17139	AUUUAUCUAUGGGCAAAUA	2603
17139	UGUAGUAGAAUCAUACCUG	953	17139	UGUAGUAGAAUCAUACCUG	953	17157	CAGGUAUGAUUCUACUACA	2604
17157	GCGCGUGCGCGCGUAGAGU	954	17157	GCGCGUGCGCGCGUAGAGU	954	17175	ACUCUACGCGCGCACGCGC	2605
17175	UGUUUUGAUAAAUUCAAAG	955	17175	UGUUUUGAUAAAUUCAAAG	955	17193	CUUUGAAUUUAUCAAAACA	2606
17193	GUGAAUUCAACACUAGAAC	956	17193	GUGAAUUCAACACUAGAAC	956	17211	GUUCUAGUGUUGAAUUCAC	2607
17211	CAGUAUGUUUUCUGCACUG	957	17211	CAGUAUGUUUUCUGCACUG	957	17229	CAGUGCAGAAAACAUACUG	2608
17229	GUAAAUGCAUUGCCAGAAA	958	17229	GUAAAUGCAUUGCCAGAAA	958	17247	UUUCUGGCAAUGCAUUUAC	2609
17247	ACAACUGCUGACAUUGUAG	959	17247	ACAACUGCUGACAUUGUAG	959	17265	CUACAAUGUCAGCAGUUGU	2610
17265	GUCUUUGAUGAAAUCUCUA	960	17265	GUCUUUGAUGAAAUCUCUA	960	17283	UAGAGAUUUCAUCAAAGAC	2611

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17283	AUGGCUACUAAUUAUGACU	961	17283	AUGGCUACUAAUUAUGACU	961	17301	AGUCAUAAUUAGUAGCCAU	2612
17301	UUGAGUGUUGUCAAUGCUA	962	17301	UUGAGUGUUGUCAAUGCUA	962	17319	UAGCAUUGACAACACUCAA	2613
17319	AGACUUCGUGCAAAACACU	963	17319	AGACUUCGUGCAAAACACU	963	17337	AGUGUUUUGCACGAAGUCU	2614
17337	UACGUCUAUAUUGGCGAUC	964	17337	UACGUCUAUAUUGGCGAUC	964	17355	GAUCGCCAAUAUAGACGUA	2615
17355	CCUGCUCAAUUACCAGCCC	965	17355	CCUGCUCAAUUACCAGCCC	965	17373	GGGCUGGUAAUUGAGCAGG	2616
17373	CCCCGCACAUUGCUGACUA	966	17373	CCCCGCACAUUGCUGACUA	966	17391	UAGUCAGCAAUGUGCGGGG	2617
17391	AAAGGCACACUAGAACCAG	967	17391	AAAGGCACACUAGAACCAG	967	17409	CUGGUUCUAGUGUGCCUUU	2618
17409	GAAUAUUUUAAUUCAGUGU	968	17409	GAAUAUUUUAAUUCAGUGU	968	17427	ACACUGAAUUAAAAUAUUC	2619
17427	UGCAGACUUAUGAAAACAA	969	17427	UGCAGACUUAUGAAAACAA	969	17445	UUGUUUUCAUAAGUCUGCA	2620
17445	AUAGGUCCAGACAUGUUCC	970	17445	AUAGGUCCAGACAUGUUCC	970	17463	GGAACAUGUCUGGACCUAU	2621
17463	CUUGGAACUUGUCGCCGUU	971	17463	CUUGGAACUUGUCGCCGUU	971	17481	AACGGCGACAAGUUCCAAG	2622
17481	UGUCCUGCUGAAAUUGUUG	972	17481	UGUCCUGCUGAAAUUGUUG	972	17499	CAACAAUUUCAGCAGGACA	2623
17499	GACACUGUGAGUGCUUUAG	973	17499	GACACUGUGAGUGCUUUAG	973	17517	CUAAAGCACUCACAGUGUC	2624
17517	GUUUAUGACAAUAAGCUAA	974	17517	GUUUAUGACAAUAAGCUAA	974	17535	UUAGCUUAUUGUCAUAAAC	2625
17535	AAAGCACACAAGGAUAAGU	975	17535	AAAGCACACAAGGAUAAGU	975	17553	ACUUAUCCUUGUGUGCUUU	2626
17553	UCAGCUCAAUGCUUCAAAA	976	17553	UCAGCUCAAUGCUUCAAAA	976	17571	UUUUGAAGCAUUGAGCUGA	2627
17571	AUGUUCUACAAAGGUGUUA	977	17571	AUGUUCUACAAAGGUGUUA	977	17589	UAACACCUUUGUAGAACAU	2628
17589	AUUACACAUGAUGUUUCAU	978	17589	AUUACACAUGAUGUUUCAU	978	17607	AUGAAACAUCAUGUGUAAU	2629
17607	UCUGCAAUCAACAGACCUC	979	17607	UCUGCAAUCAACAGACCUC	979	17625	GAGGUCUGUUGAUUGCAGA	2630
17625	CAAAUAGGCGUUGUAAGAG	980	17625	CAAAUAGGCGUUGUAAGAG	980	17643	CUCUUACAACGCCUAUUUG	2631
17643	GAAUUUCUUACACGCAAUC	981	17643	GAAUUUCUUACACGCAAUC	981	17661	GAUUGCGUGUAAGAAAUUC	2632
17661	CCUGCUUGGAGAAAAGCUG	982	17661	CCUGCUUGGAGAAAAGCUG	982	17679	CAGCUUUUCUCCAAGCAGG	2633
17679	GUUUUUAUCUCACCUUAUA	983	17679	GUUUUUAUCUCACCUUAUA	983	17697	UAUAAGGUGAGAUAAAAAC	2634
17697	AAUUCACAGAACGCUGUAG	984	17697	AAUUCACAGAACGCUGUAG	984	17715	CUACAGCGUUCUGUGAAUU	2635
17715	GCUUCAAAAAUCUUAGGAU	985	17715	GCUUCAAAAAUCUUAGGAU	985	17733	AUCCUAAGAUUUUUGAAGC	2636
17733	UUGCCUACGCAGACUGUUG	986	17733	UUGCCUACGCAGACUGUUG	986	17751	CAACAGUCUGCGUAGGCAA	2637
17751	GAUUCAUCACAGGGUUCUG	987	17751	GAUUCAUCACAGGGUUCUG	987	17769	CAGAACCCUGUGAUGAAUC	2638
17769	GAAUAUGACUAUGUCAUAU	988	17769	GAAUAUGACUAUGUCAUAU	988	17787	AUAUGACAUAGUCAUAUUC	2639
17787	UUCACACAAACUACUGAAA	989	17787	UUCACACAAACUACUGAAA	989	17805	UUUCAGUAGUUUGUGUGAA	2640
17805	ACAGCACACUCUUGUAAUG	990	17805	ACAGCACACUCUUGUAAUG	990	17823	CAUUACAAGAGUGUGCUGU	2641
17823	GUCAACCGCUUCAAUGUGG	991	17823	GUCAACCGCUUCAAUGUGG	991	17841	CCACAUUGAAGCGGUUGAC	2642
17841	GCUAUCACAAGGGCAAAAA	992	17841	GCUAUCACAAGGGCAAAAA	992	17859	UUUUUGCCCUUGUGAUAGC	2643
17859	AUUGGCAUUUUGUGCAUAA	993	17859	AUUGGCAUUUUGUGCAUAA	993	17877	UUAUGCACAAAAUGCCAAU	2644
17877	AUGUCUGAUAGAGAUCUUU	994	17877	AUGUCUGAUAGAGAUCUUU	994	17895	AAAGAUCUCUAUCAGACAU	2645
17895	UAUGACAAACUGCAAUUUA	995	17895	UAUGACAAACUGCAAUUUA	995	17913	UAAAUUGCAGUUUGUCAUA	2646
17913	ACAAGUCUAGAAAUACCAC	996	17913	ACAAGUCUAGAAAUACCAC	996	17931	GUGGUAUUUCUAGACUUGU	2647
17931	CGUCGCAAUGUGGCUACAU	997	17931	CGUCGCAAUGUGGCUACAU	997	17949	AUGUAGCCACAUUGCGACG	2648
17949	UUACAAGCAGAAAAUGUAA	998	17949	UUACAAGCAGAAAAUGUAA	998	17967	UUACAUUUUCUGCUUGUAA	2649
17967	ACUGGACUUUUUAAGGACU	999	17967	ACUGGACUUUUUAAGGACU	999	17985	AGUCCUUAAAAAGUCCAGU	2650
17985	UGUAGUAAGAUCAUUACUG	1000	17985	UGUAGUAAGAUCAUUACUG	1000	18003	CAGUAAUGAUCUUACUACA	2651
18003	GGUCUUCAUCCUACACAGG	1001	18003	GGUCUUCAUCCUACACAGG	1001	18021	CCUGUGUAGGAUGAAGACC	2652
18021	GCACCUACACACCUCAGCG	1002	18021	GCACCUACACACCUCAGCG	1002	18039	CGCUGAGGUGUGUAGGUGC	2653

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18039	GUUGAUAUAAAGUUCAAGA	1003	18039	GUUGAUAUAAAGUUCAAGA	1003	18057	UCUUGAACUUUAUAUCAAC	2654
18057	ACUGAAGGAUUAUGUGUUG	1004	18057	ACUGAAGGAUUAUGUGUUG	1004	18075	CAACACAUAAUCCUUCAGU	2655
18075	GACAUACCAGGCAUACCAA	1005	18075	GACAUACCAGGCAUACCAA	1005	18093	UUGGUAUGCCUGGUAUGUC	2656
18093	AAGGACAUGACCUACCGUA	1006	18093	AAGGACAUGACCUACCGUA	1006	18111	UACGGUAGGUCAUGUCCUU	2657
18111	AGACUCAUCUCUAUGAUGG	1007	18111	AGACUCAUCUCUAUGAUGG	1007	18129	CCAUCAUAGAGAUGAGUCU	2658
18129	GGUUUCAAAAUGAAUUACC	1008	18129	GGUUUCAAAAUGAAUUACC	1008	18147	GGUAAUUCAUUUUGAAACC	2659
18147	CAAGUCAAUGGUUACCCUA	1009	18147	CAAGUCAAUGGUUACCCUA	1009	18165	UAGGGUAACCAUUGACUUG	2660
18165	AAUAUGUUUAUCACCCGCG	1010	18165	AAUAUGUUUAUCACCCGCG	1010	18183	CGCGGGUGAUAAACAUAUU	2661
18183	GAAGAAGCUAUUCGUCACG	1011	18183	GAAGAAGCUAUUCGUCACG	1011	18201	CGUGACGAAUAGCUUCUUC	2662
18201	GUUCGUGCGUGGAUUGGCU	1012	18201	GUUCGUGCGUGGAUUGGCU	1012	18219	AGCCAAUCCACGCACGAAC	2663
18219	UUUGAUGUAGAGGGCUGUC	1013	18219	UUUGAUGUAGAGGGCUGUC	1013	18237	GACAGCCCUCUACAUCAAA	2664
18237	CAUGCAACUAGAGAUGCUG	1014	18237	CAUGCAACUAGAGAUGCUG	1014	18255	CAGCAUCUCUAGUUGCAUG	2665
18255	GUGGGUACUAACCUACCUC	1015	18255	GUGGGUACUAACCUACCUC	1015	18273	GAGGUAGGUUAGUACCCAC	2666
18273	CUCCAGCUAGGAUUUUCUA	1016	18273	CUCCAGCUAGGAUUUUCUA	1016	18291	UAGAAAAUCCUAGCUGGAG	2667
18291	ACAGGUGUUAACUUAGUAG	1017	18291	ACAGGUGUUAACUUAGUAG	1017	18309	CUACUAAGUUAACACCUGU	2668
18309	GCUGUACCGACUGGUUAUG	1018	18309	GCUGUACCGACUGGUUAUG	1018	18327	CAUAACCAGUCGGUACAGC	2669
18327	GUUGACACUGAAAAUAACA	1019	18327	GUUGACACUGAAAAUAACA	1019	18345	UGUUAUUUUCAGUGUCAAC	2670
18345	ACAGAAUUCACCAGAGUUA	1020	18345	ACAGAAUUCACCAGAGUUA	1020	18363	UAACUCUGGUGAAUUCUGU	2671
18363	AAUGCAAAACCUCCACCAG	1021	18363	AAUGCAAAACCUCCACCAG	1021	18381	CUGGUGGAGGUUUUGCAUU	2672
18381	GGUGACCAGUUUAAACAUC	1022	18381	GGUGACCAGUUUAAACAUC	1022	18399	GAUGUUUAAACUGGUCACC	2673
18399	CUUAUACCACUCAUGUAUA	1023	18399	CUUAUACCACUCAUGUAUA	1023	18417	UAUACAUGAGUGGUAUAAG	2674
18417	AAAGGCUUGCCCUGGAAUG	1024	18417	AAAGGCUUGCCCUGGAAUG	1024	18435	CAUUCCAGGGCAAGCCUUU	2675
18435	GUAGUGCGUAUUAAGAUAG	1025	18435	GUAGUGCGUAUUAAGAUAG	1025	18453	CUAUCUUAAUACGCACUAC	2676
18453	GUACAAAUGCUCAGUGAUA	1026	18453	GUACAAAUGCUCAGUGAUA	1026	18471	UAUCACUGAGCAUUUGUAC	2677
18471	ACACUGAAAGGAUUGUCAG	1027	18471	ACACUGAAAGGAUUGUCAG	1027	18489	CUGACAAUCCUUUCAGUGU	2678
18489	GACAGAGUCGUGUUCGUCC	1028	18489	GACAGAGUCGUGUUCGUCC	1028	18507	GGACGAACACGACUCUGUC	2679
18507	CUUUGGGCGCAUGGCUUUG	1029	18507	CUUUGGGCGCAUGGCUUUG	1029	18525	CAAAGCCAUGCGCCCAAAG	2680
18525	GAGCUUACAUCAAUGAAGU	1030	18525	GAGCUUACAUCAAUGAAGU	1030	18543	ACUUCAUUGAUGUAAGCUC	2681
18543	UACUUUGUCAAGAUUGGAC	1031	18543	UACUUUGUCAAGAUUGGAC	1031	18561	GUCCAAUCUUGACAAAGUA	2682
18561	CCUGAAAGAACGUGUUGUC	1032	18561	CCUGAAAGAACGUGUUGUC	1032	18579	GACAACACGUUCUUUCAGG	2683
18579	CUGUGUGACAAACGUGCAA	1033	18579	CUGUGUGACAAACGUGCAA	1033	18597	UUGCACGUUUGUCACACAG	2684
18597	ACUUGCUUUUCUACUUCAU	1034	18597	ACUUGCUUUUCUACUUCAU	1034	18615	AUGAAGUAGAAAAGCAAGU	2685
18615	UCAGAUACUUAUGCCUGCU	1035	18615	UCAGAUACUUAUGCCUGCU	1035	18633	AGCAGGCAUAAGUAUCUGA	2686
18633	UGGAAUCAUUCUGUGGGUU	1036	18633	UGGAAUCAUUCUGUGGGUU	1036	18651	AACCCACAGAAUGAUUCCA	2687
18651	UUUGACUAUGUCUAUAACC	1037	18651	UUUGACUAUGUCUAUAACC	1037	18669	GGUUAUAGACAUAGUCAAA	2688
18669	CCAUUUAUGAUUGAUGUUC	1038	18669	CCAUUUAUGAUUGAUGUUC	1038	18687	GAACAUCAAUCAUAAAUGG	2689
18687	CAGCAGUGGGGCUUUACGG	1039	18687	CAGCAGUGGGGCUUUACGG	1039	18705	CCGUAAAGCCCCACUGCUG	2690
18705	GGUAACCUUCAGAGUAACC	1040	18705	GGUAACCUUCAGAGUAACC	1040	18723	GGUUACUCUGAAGGUUACC	2691
18723	CAUGACCAACAUUGCCAGG	1041	18723	CAUGACCAACAUUGCCAGG	1041	18741	CCUGGCAAUGUUGGUCAUG	2692
18741	GUACAUGGAAAUGCACAUG	1042	18741	GUACAUGGAAAUGCACAUG	1042	18759	CAUGUGCAUUUCCAUGUAC	2693
18759	GUGGCUAGUUGUGAUGCUA	1043	18759	GUGGCUAGUUGUGAUGCUA	1043	18777	UAGCAUCACAACUAGCCAC	2694
18777	AUCAUGACUAGAUGUUUAG	1044	18777	AUCAUGACUAGAUGUUUAG	1044	18795	CUAAACAUCUAGUCAUGAU	2695

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18795	GCAGUCCAUGAGUGCUUUG	1045	18795	GCAGUCCAUGAGUGCUUUG	1045	18813	CAAAGCACUCAUGGACUGC	2696
18813	GUUAAGCGCGUUGAUUGGU	1046	18813	GUUAAGCGCGUUGAUUGGU	1046	18831	ACCAAUCAACGCGCUUAAC	2697
18831	UCUGUUGAAUACCCUAUUA	1047	18831	UCUGUUGAAUACCCUAUUA	1047	18849	UAAUAGGGUAUUCAACAGA	2698
18849	AUAGGAGAUGAACUGAGGG	1048	18849	AUAGGAGAUGAACUGAGGG	1048	18867	CCCUCAGUUCAUCUCCUAU	2699
18867	GUUAAUUCUGCUUGCAGAA	1049	18867	GUUAAUUCUGCUUGCAGAA	1049	18885	UUCUGCAAGCAGAAUUAAC	2700
18885	AAAGUACAACACAUGGUUG	1050	18885	AAAGUACAACACAUGGUUG	1050	18903	CAACCAUGUGUUGUACUUU	2701
18903	GUGAAGUCUGCAUUGCUUG	1051	18903	GUGAAGUCUGCAUUGCUUG	1051	18921	CAAGCAAUGCAGACUUCAC	2702
18921	GCUGAUAAGUUUCCAGUUC	1052	18921	GCUGAUAAGUUUCCAGUUC	1052	18939	GAACUGGAAACUUAUCAGC	2703
18939	CUUCAUGACAUUGGAAAUC	1053	18939	CUUCAUGACAUUGGAAAUC	1053	18957	GAUUUCCAAUGUCAUGAAG	2704
18957	CCAAAGGCUAUCAAGUGUG	1054	18957	CCAAAGGCUAUCAAGUGUG	1054	18975	CACACUUGAUAGCCUUUGG	2705
18975	GUGCCUCAGGCUGAAGUAG	1055	18975	GUGCCUCAGGCUGAAGUAG	1055	18993	CUACUUCAGCCUGAGGCAC	2706
18993	GAAUGGAAGUUCUACGAUG	1056	18993	GAAUGGAAGUUCUACGAUG	1056	19011	CAUCGUAGAACUUCCAUUC	2707
19011	GCUCAGCCAUGUAGUGACA	1057	19011	GCUCAGCCAUGUAGUGACA	1057	19029	UGUCACUACAUGGCUGAGC	2708
19029	AAAGCUUACAAAAUAGAGG	1058	19029	AAAGCUUACAAAAUAGAGG	1058	19047	CCUCUAUUUUGUAAGCUUU	2709
19047	GAACUCUUCUAUUCUUAUG	1059	19047	GAACUCUUCUAUUCUUAUG	1059	19065	CAUAAGAAUAGAAGAGUUC	2710
19065	GCUACACAUCACGAUAAAU	1060	19065	GCUACACAUCACGAUAAAU	1060	19083	AUUUAUCGUGAUGUGUAGC	2711
19083	UUCACUGAUGGUGUUUGUU	1061	19083	UUCACUGAUGGUGUUUGUU	1061	19101	AACAAACACCAUCAGUGAA	2712
19101	UUGUUUUGGAAUUGUAACG	1062	19101	UUGUUUUGGAAUUGUAACG	1062	19119	CGUUACAAUUCCAAAACAA	2713
19119	GUUGAUCGUUACCCAGCCA	1063	19119	GUUGAUCGUUACCCAGCCA	1063	19137	UGGCUGGGUAACGAUCAAC	2714
19137	AAUGCAAUUGUGUGUAGGU	1064	19137	AAUGCAAUUGUGUGUAGGU	1064	19155	ACCUACACACAAUUGCAUU	2715
19155	UUUGACACAAGAGUCUUGU	1065	19155	UUUGACACAAGAGUCUUGU	1065	19173	ACAAGACUCUUGUGUCAAA	2716
19173	UCAAACUUGAACUUACCAG	1066	19173	UCAAACUUGAACUUACCAG	1066	19191	CUGGUAAGUUCAAGUUUGA	2717
19191	GGCUGUGAUGGUGGUAGUU	1067	19191	GGCUGUGAUGGUGGUAGUU	1067	19209	AACUACCACCAUCACAGCC	2718
19209	UUGUAUGUGAAUAAGCAUG	1068	19209	UUGUAUGUGAAUAAGCAUG	1068	19227	CAUGCUUAUUCACAUACAA	2719
19227	GCAUUCCACACUCCAGCUU	1069	19227	GCAUUCCACACUCCAGCUU	1069	19245	AAGCUGGAGUGUGGAAUGC	2720
19245	UUCGAUAAAAGUGCAUUUA	1070	19245	UUCGAUAAAAGUGCAUUUA	1070	19263	UAAAUGCACUUUUAUCGAA	2721
19263	ACUAAUUUAAAGCAAUUGC	1071	19263	ACUAAUUUAAAGCAAUUGC	1071	19281	GCAAUUGCUUUAAAUUAGU	2722
19281	CCUUUCUUUUACUAUUCUG	1072	19281	CCUUUCUUUUACUAUUCUG	1072	19299	CAGAAUAGUAAAAGAAAGG	2723
19299	GAUAGUCCUUGUGAGUCUC	1073	19299	GAUAGUCCUUGUGAGUCUC	1073	19317	GAGACUCACAAGGACUAUC	2724
19317	CAUGGCAAACAAGUAGUGU	1074	19317	CAUGGCAAACAAGUAGUGU	1074	19335	ACACUACUUGUUUGCCAUG	2725
19335	UCGGAUAUUGAUUAUGUUC	1075	19335	UCGGAUAUUGAUUAUGUUC	1075	19353	GAACAUAAUCAAUAUCCGA	2726
19353	CCACUCAAAUCUGCUACGU	1076	19353	CCACUCAAAUCUGCUACGU	1076	19371	ACGUAGCAGAUUUGAGUGG	2727
19371	UGUAUUACACGAUGCAAUU	1077	19371	UGUAUUACACGAUGCAAUU	1077	19389	AAUUGCAUCGUGUAAUACA	2728
19389	UUAGGUGGUGCUGUUUGCA	1078	19389	UUAGGUGGUGCUGUUUGCA	1078	19407	UGCAAACAGCACCACCUAA	2729
19407	AGACACCAUGCAAAUGAGU	1079	19407	AGACACCAUGCAAAUGAGU	1079	19425	ACUCAUUUGCAUGGUGUCU	2730
19425	UACCGACAGUACUUGGAUG	1080	19425	UACCGACAGUACUUGGAUG	1080	19443	CAUCCAAGUACUGUCGGUA	2731
19443	GCAUAUAAUAUGAUGAUUU	1081	19443	GCAUAUAAUAUGAUGAUUU	1081	19461	AAAUCAUCAUAUUAUAUGC	2732
19461	UCUGCUGGAUUUAGCCUAU	1082	19461	UCUGCUGGAUUUAGCCUAU	1082	19479	AUAGGCUAAAUCCAGCAGA	2733
19479	UGGAUUUACAAACAAUUUG	1083	19479	UGGAUUUACAAACAAUUUG	1083	19497	CAAAUUGUUUGUAAAUCCA	2734
19497	GAUACUUAUAACCUGUGGA	1084	19497	GAUACUUAUAACCUGUGGA	1084	19515	UCCACAGGUUAUAAGUAUC	2735
19515	AAUACAUUUACCAGGUUAC	1085	19515	AAUACAUUUACCAGGUUAC	1085	19533	GUAACCUGGUAAAUGUAUU	2736
19533	CAGAGUUUAGAAAAUGUGG	1086	19533	CAGAGUUUAGAAAAUGUGG	1086	19551	CCACAUUUUCUAAACUCUG	2737

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19551	GCUUAUAAUGUUGUUAAUA	1087	19551	GCUUAUAAUGUUGUUAAUA	1087	19569	UAUUAACAACAUUAUAAGC	2738
19569	AAAGGACACUUUGAUGGAC	1088	19569	AAAGGACACUUUGAUGGAC	1088	19587	GUCCAUCAAAGUGUCCUUU	2739
19587	CACGCCGGCGAAGCACCUG	1089	19587	CACGCCGGCGAAGCACCUG	1089	19605	CAGGUGCUUCGCCGGCGUG	2740
19605	GUUUCCAUCAUUAAUAAUG	1090	19605	GUUUCCAUCAUUAAUAAUG	1090	19623	CAUUAUUAAUGAUGGAAAC	2741
19623	GCUGUUUACACAAAGGUAG	1091	19623	GCUGUUUACACAAAGGUAG	1091	19641	CUACCUUUGUGUAAACAGC	2742
19641	GAUGGUAUUGAUGUGGAGA	1092	19641	GAUGGUAUUGAUGUGGAGA	1092	19659	UCUCCACAUCAAUACCAUC	2743
19659	AUCUUUGAAAAUAAGACAA	1093	19659	AUCUUUGAAAAUAAGACAA	1093	19677	UUGUCUUAUUUUCAAAGAU	2744
19677	ACACUUCCUGUUAAUGUUG	1094	19677	ACACUUCCUGUUAAUGUUG	1094	19695	CAACAUUAACAGGAAGUGU	2745
19695	GCAUUUGAGCUUUGGGCUA	1095	19695	GCAUUUGAGCUUUGGGCUA	1095	19713	UAGCCCAAAGCUCAAAUGC	2746
19713	AAGCGUAACAUUAAACCAG	1096	19713	AAGCGUAACAUUAAACCAG	1096	19731	CUGGUUUAAUGUUACGCUU	2747
19731	GUGCCAGAGAUUAAGAUAC	1097	19731	GUGCCAGAGAUUAAGAUAC	1097	19749	GUAUCUUAAUCUCUGGCAC	2748
19749	CUCAAUAAUUUGGGUGUUG	1098	19749	CUCAAUAAUUUGGGUGUUG	1098	19767	CAACACCCAAAUUAUUGAG	2749
19767	GAUAUCGCUGCUAAUACUG	1099	19767	GAUAUCGCUGCUAAUACUG	1099	19785	CAGUAUUAGCAGCGAUAUC	2750
19785	GUAAUCUGGGACUACAAAA	1100	19785	GUAAUCUGGGACUACAAAA	1100	19803	UUUUGUAGUCCCAGAUUAC	2751
19803	AGAGAAGCCCCAGCACAUG	1101	19803	AGAGAAGCCCCAGCACAUG	1101	19821	CAUGUGCUGGGGCUUCUCU	2752
19821	GUAUCUACAAUAGGUGUCU	1102	19821	GUAUCUACAAUAGGUGUCU	1102	19839	AGACACCUAUUGUAGAUAC	2753
19839	UGCACAAUGACUGACAUUG	1103	19839	UGCACAAUGACUGACAUUG	1103	19857	CAAUGUCAGUCAUUGUGCA	2754
19857	GCCAAGAAACCUACUGAGA	1104	19857	GCCAAGAAACCUACUGAGA	1104	19875	UCUCAGUAGGUUUCUUGGC	2755
19875	AGUGCUUGUUCUUCACUUA	1105	19875	AGUGCUUGUUCUUCACUUA	1105	19893	UAAGUGAAGAACAAGCACU	2756
19893	ACUGUCUUGUUUGAUGGUA	1106	19893	ACUGUCUUGUUUGAUGGUA	1106	19911	UACCAUCAAACAAGACAGU	2757
19911	AGAGUGGAAGGACAGGUAG	1107	19911	AGAGUGGAAGGACAGGUAG	1107	19929	CUACCUGUCCUUCCACUCU	2758
19929	GACCUUUUUAGAAACGCCC	1108	19929	GACCUUUUUAGAAACGCCC	1108	19947	GGGCGUUUCUAAAAAGGUC	2759
19947	CGUAAUGGUGUUUUAAUAA	1109	19947	CGUAAUGGUGUUUUAAUAA	1109	19965	UUAUUAAAACACCAUUACG	2760
19965	ACAGAAGGUUCAGUCAAAG	1110	19965	ACAGAAGGUUCAGUCAAAG	1110	19983	CUUUGACUGAACCUUCUGU	2761
19983	GGUCUAACACCUUCAAAGG	1111	19983	GGUCUAACACCUUCAAAGG	1111	20001	CCUUUGAAGGUGUUAGACC	2762
20001	GGACCAGCACAAGCUAGCG	1112	20001	GGACCAGCACAAGCUAGCG	1112	20019	CGCUAGCUUGUGCUGGUCC	2763
20019	GUCAAUGGAGUCACAUUAA	1113	20019	GUCAAUGGAGUCACAUUAA	1113	20037	UUAAUGUGACUCCAUUGAC	2764
20037	AUUGGAGAAUCAGUAAAAA	1114	20037	AUUGGAGAAUCAGUAAAAA	1114	20055	UUUUUACUGAUUCUCCAAU	2765
20055	ACACAGUUUAACUACUUUA	1115	20055	ACACAGUUUAACUACUUUA	1115	20073	UAAAGUAGUUAAACUGUGU	2766
20073	AAGAAAGUAGACGGCAUUA	1116	20073	AAGAAAGUAGACGGCAUUA	1116	20091	UAAUGCCGUCUACUUUCUU	2767
20091	AUUCAACAGUUGCCUGAAA	1117	20091	AUUCAACAGUUGCCUGAAA	1117	20109	UUUCAGGCAACUGUUGAAU	2768
20109	ACCUACUUUACUCAGAGCA	1118	20109	ACCUACUUUACUCAGAGCA	1118	20127	UGCUCUGAGUAAAGUAGGU	2769
20127	AGAGACUUAGAGGAUUUUA	1119	20127	AGAGACUUAGAGGAUUUUA	1119	20145	UAAAAUCCUCUAAGUCUCU	2770
20145	AAGCCCAGAUCACAAAUGG	1120	20145	AAGCCCAGAUCACAAAUGG	1120	20163	CCAUUUGUGAUCUGGGCUU	2771
20163	GAAACUGACUUUCUCGAGC	1121	20163	GAAACUGACUUUCUCGAGC	1121	20181	GCUCGAGAAAGUCAGUUUC	2772
20181	CUCGCUAUGGAUGAAUUCA	1122	20181	CUCGCUAUGGAUGAAUUCA	1122	20199	UGAAUUCAUCCAUAGCGAG	2773
20199	AUACAGCGAUAUAAGCUCG	1123	20199	AUACAGCGAUAUAAGCUCG	1123	20217	CGAGCUUAUAUCGCUGUAU	2774
20217	GAGGGCUAUGCCUUCGAAC	1124	20217	GAGGGCUAUGCCUUCGAAC	1124	20235	GUUCGAAGGCAUAGCCCUC	2775
20235	CACAUCGUUUAUGGAGAUU	1125	20235	CACAUCGUUUAUGGAGAUU	1125	20253	AAUCUCCAUAAACGAUGUG	2776
20253	UUCAGUCAUGGACAACUUG	1126	20253	UUCAGUCAUGGACAACUUG	1126	20271	CAAGUUGUCCAUGACUGAA	2777
20271	GGCGGUCUUCAUUUAAUGA	1127	20271	GGCGGUCUUCAUUUAAUGA	1127	20289	UCAUUAAAUGAAGACCGCC	2778
20289	AUAGGCUUAGCCAAGCGCU	1128	20289	AUAGGCUUAGCCAAGCGCU	1128	20307	AGCGCUUGGCUAAGCCUAU	2779

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20307	UCACAAGAUUCACCACUUA	1129	20307	UCACAAGAUUCACCACUUA	1129	20325	UAAGUGGUGAAUCUUGUGA	2780
20325	AAAUUAGAGGAUUUUAUCC	1130	20325	AAAUUAGAGGAUUUUAUCC	1130	20343	GGAUAAAAUCCUCUAAUUU	2781
20343	CCUAUGGACAGCACAGUGA	1131	20343	CCUAUGGACAGCACAGUGA	1131	20361	UCACUGUGCUGUCCAUAGG	2782
20361	AAAAAUUACUUCAUAACAG	1132	20361	AAAAAUUACUUCAUAACAG	1132	20379	CUGUUAUGAAGUAAUUUUU	2783
20379	GAUGCGCAAACAGGUUCAU	1133	20379	GAUGCGCAAACAGGUUCAU	1133	20397	AUGAACCUGUUUGCGCAUC	2784
20397	UCAAAAUGUGUGUGUUCUG	1134	20397	UCAAAAUGUGUGUGUUCUG	1134	20415	CAGAACACACACAUUUUGA	2785
20415	GUGAUUGAUCUUUUACUUG	1135	20415	GUGAUUGAUCUUUUACUUG	1135	20433	CAAGUAAAAGAUCAAUCAC	2786
20433	GAUGACUUUGUCGAGAUAA	1136	20433	GAUGACUUUGUCGAGAUAA	1136	20451	UUAUCUCGACAAAGUCAUC	2787
20451	AUAAAGUCACAAGAUUUGU	1137	20451	AUAAAGUCACAAGAUUUGU	1137	20469	ACAAAUCUUGUGACUUUAU	2788
20469	UCAGUGAUUUCAAAAGUGG	1138	20469	UCAGUGAUUUCAAAAGUGG	1138	20487	CCACUUUUGAAAUCACUGA	2789
20487	GUCAAGGUUACAAUUGACU	1139	20487	GUCAAGGUUACAAUUGACU	1139	20505	AGUCAAUUGUAACCUUGAC	2790
20505	UAUGCUGAAAUUUCAUUCA	1140	20505	UAUGCUGAAAUUUCAUUCA	1140	20523	UGAAUGAAAUUUCAGCAUA	2791
20523	AUGCUUUGGUGUAAGGAUG	1141	20523	AUGCUUUGGUGUAAGGAUG	1141	20541	CAUCCUUACACCAAAGCAU	2792
20541	GGACAUGUUGAAACCUUCU	1142	20541	GGACAUGUUGAAACCUUCU	1142	20559	AGAAGGUUUCAACAUGUCC	2793
20559	UACCCAAAACUACAAGCAA	1143	20559	UACCCAAAACUACAAGCAA	1143	20577	UUGCUUGUAGUUUUGGGUA	2794
20577	AGUCGAGCGUGGCAACCAG	1144	20577	AGUCGAGCGUGGCAACCAG	1144	20595	CUGGUUGCCACGCUCGACU	2795
20595	GGUGUUGCGAUGCCUAACU	1145	20595	GGUGUUGCGAUGCCUAACU	1145	20613	AGUUAGGCAUCGCAACACC	2796
20613	UUGUACAAGAUGCAAAGAA	1146	20613	UUGUACAAGAUGCAAAGAA	1146	20631	UUCUUUGCAUCUUGUACAA	2797
20631	AUGCUUCUUGAAAAGUGUG	1147	20631	AUGCUUCUUGAAAAGUGUG	1147	20649	CACACUUUUCAAGAAGCAU	2798
20649	GACCUUCAGAAUUAUGGUG	1148	20649	GACCUUCAGAAUUAUGGUG	1148	20667	CACCAUAAUUCUGAAGGUC	2799
20667	GAAAAUGCUGUUAUACCAA	1149	20667	GAAAAUGCUGUUAUACCAA	1149	20685	UUGGUAUAACAGCAUUUUC	2800
20685	AAAGGAAUAAUGAUGAAUG	1150	20685	AAAGGAAUAAUGAUGAAUG	1150	20703	CAUUCAUCAUUAUUCCUUU	2801
20703	GUCGCAAAGUAUACUCAAC	1151	20703	GUCGCAAAGUAUACUCAAC	1151	20721	GUUGAGUAUACUUUGCGAC	2802
20721	CUGUGUCAAUACUUAAAUA	1152	20721	CUGUGUCAAUACUUAAAUA	1152	20739	UAUUUAAGUAUUGACACAG	2803
20739	ACACUUACUUUAGCUGUAC	1153	20739	ACACUUACUUUAGCUGUAC	1153	20757	GUACAGCUAAAGUAAGUGU	2804
20757	CCCUACAACAUGAGAGUUA	1154	20757	CCCUACAACAUGAGAGUUA	1154	20775	UAACUCUCAUGUUGUAGGG	2805
20775	AUUCACUUUGGUGCUGGCU	1155	20775	AUUCACUUUGGUGCUGGCU	1155	20793	AGCCAGCACCAAAGUGAAU	2806
20793	UCUGAUAAAGGAGUUGCAC	1156	20793	UCUGAUAAAGGAGUUGCAC	1156	20811	GUGCAACUCCUUUAUCAGA	2807
20811	CCAGGUACAGCUGUGCUCA	1157	20811	CCAGGUACAGCUGUGCUCA	1157	20829	UGAGCACAGCUGUACCUGG	2808
20829	AGACAAUGGUUGCCAACUG	1158	20829	AGACAAUGGUUGCCAACUG	1158	20847	CAGUUGGCAACCAUUGUCU	2809
20847	GGCACACUACUUGUCGAUU	1159	20847	GGCACACUACUUGUCGAUU	1159	20865	AAUCGACAAGUAGUGUGCC	2810
20865	UCAGAUCUUAAUGACUUCG	1160	20865	UCAGAUCUUAAUGACUUCG	1160	20883	CGAAGUCAUUAAGAUCUGA	2811
20883	GUCUCCGACGCAUAUUCUA	1161	20883	GUCUCCGACGCAUAUUCUA	1161	20901	UAGAAUAUGCGUCGGAGAC	2812
20901	ACUUUAAUUGGAGACUGUG	1162	20901	ACUUUAAUUGGAGACUGUG	1162	20919	CACAGUCUCCAAUUAAAGU	2813
20919	GCAACAGUACAUACGGCUA	1163	20919	GCAACAGUACAUACGGCUA	1163	20937	UAGCCGUAUGUACUGUUGC	2814
20937	AAUAAAUGGGACCUUAUUA	1164	20937	AAUAAAUGGGACCUUAUUA	1164	20955	UAAUAAGGUCCCAUUUAUU	2815
20955	AUUAGCGAUAUGUAUGACC	1165	20955	AUUAGCGAUAUGUAUGACC	1165	20973	GGUCAUACAUAUCGCUAAU	2816
20973	CCUAGGACCAAACAUGUGA	1166	20973	CCUAGGACCAAACAUGUGA	1166	20991	UCACAUGUUUGGUCCUAGG	2817
20991	ACAAAAGAGAAUGACUCUA	1167	20991	ACAAAAGAGAAUGACUCUA	1167	21009	UAGAGUCAUUCUCUUUUGU	2818
21009	AAAGAAGGGUUUUUCACUU	1168	21009	AAAGAAGGGUUUUUCACUU	1168	21027	AAGUGAAAAACCCUUCUUU	2819
21027	UAUCUGUGUGGAUUUAUAA	1169	21027	UAUCUGUGUGGAUUUAUAA	1169	21045	UUAUAAAUCCACACAGAUA	2820
21045	AAGCAAAAACUAGCCCUGG	1170	21045	AAGCAAAAACUAGCCCUGG	1170	21063	CCAGGGCUAGUUUUUGCUU	2821

21063	GGUGGUUCUAUAGCUGUAA	1171	21063	GGUGGUUCUAUAGCUGUAA	1171	21081	UUACAGCUAUAGAACCACC	2822
21081	AAGAUAACAGAGCAUUCUU	1172	21081	AAGAUAACAGAGCAUUCUU	1172	21099	AAGAAUGCUCUGUUAUCUU	2823
21099	UGGAAUGCUGACCUUUACA	1173	21099	UGGAAUGCUGACCUUUACA	1173	21117	UGUAAAGGUCAGCAUUCCA	2824
21117	AAGCUUAUGGGCCAUUUCU	1174	21117	AAGCUUAUGGGCCAUUUCU	1174	21135	AGAAAUGGCCCAUAAGCUU	2825
21135	UCAUGGUGGACAGCUUUUG	1175	21135	UCAUGGUGGACAGCUUUUG	1175	21153	CAAAAGCUGUCCACCAUGA	2826
21153	GUUACAAAUGUAAAUGCAU	1176	21153	GUUACAAAUGUAAAUGCAU	1176	21171	AUGCAUUUACAUUUGUAAC	2827
21171	UCAUCAUCGGAAGCAUUUU	1177	21171	UCAUCAUCGGAAGCAUUUU	1177	21189	AAAAUGCUUCCGAUGAUGA	2828
21189	UUAAUUGGGGCUAACUAUC	1178	21189	UUAAUUGGGGCUAACUAUC	1178	21207	GAUAGUUAGCCCCAAUUAA	2829
21207	CUUGGCAAGCCGAAGGAAC	1179	21207	CUUGGCAAGCCGAAGGAAC	1179	21225	GUUCCUUCGGCUUGCCAAG	2830
21225	CAAAUUGAUGGCUAUACCA	1180	21225	CAAAUUGAUGGCUAUACCA	1180	21243	UGGUAUAGCCAUCAAUUUG	2831
21243	AUGCAUGCUAACUACAUUU	1181	21243	AUGCAUGCUAACUACAUUU	1181	21261	AAAUGUAGUUAGCAUGCAU	2832
21261	UUCUGGAGGAACACAAAUC	1182	21261	UUCUGGAGGAACACAAAUC	1182	21279	GAUUUGUGUUCCUCCAGAA	2833
21279	CCUAUCCAGUUGUCUUCCU	1183	21279	CCUAUCCAGUUGUCUUCCU	1183	21297	AGGAAGACAACUGGAUAGG	2834
21297	UAUUCACUCUUUGACAUGA	1184	21297	UAUUCACUCUUUGACAUGA	1184	21315	UCAUGUCAAAGAGUGAAUA	2835
21315	AGCAAAUUUCCUCUUAAAU	1185	21315	AGCAAAUUUCCUCUUAAAU	1185	21333	AUUUAAGAGGAAAUUUGCU	2836
21333	UUAAGAGGAACUGCUGUAA	1186	21333	UUAAGAGGAACUGCUGUAA	1186	21351	UUACAGCAGUUCCUCUUAA	2837
21351	AUGUCUCUUAAGGAGAAUC	1187	21351	AUGUCUCUUAAGGAGAAUC	1187	21369	GAUUCUCCUUAAGAGACAU	2838
21369	CAAAUCAAUGAUAUGAUUU	1188	21369	CAAAUCAAUGAUAUGAUUU	1188	21387	AAAUCAUAUCAUUGAUUUG	2839
21387	UAUUCUCUUCUGGAAAAAG	1189	21387	UAUUCUCUUCUGGAAAAAG	1189	21405	CUUUUUCCAGAAGAGAAUA	2840
21405	GGUAGGCUUAUCAUUAGAG	1190	21405	GGUAGGCUUAUCAUUAGAG	1190	21423	CUCUAAUGAUAAGCCUACC	2841
21423	GAAAACAACAGAGUUGUGG	1191	21423	GAAAACAACAGAGUUGUGG	1191	21441	CCACAACUCUGUUGUUUUC	2842
21441	GUUUCAAGUGAUAUUCUUG	1192	21441	GUUUCAAGUGAUAUUCUUG	1192	21459	CAAGAAUAUCACUUGAAAC	2843
21459	GUUAACAACUAAACGAACA	1193	21459	GUUAACAACUAAACGAACA	1193	21477	UGUUCGUUUAGUUGUUAAC	2844
21477	AUGUUUAUUUUCUUAUUAU	1194	21477	AUGUUUAUUUUCUUAUUAU	1194	21495	AUAAUAAGAAAAUAAACAU	2845
21495	UUUCUUACUCUCACUAGUG	1195	21495	UUUCUUACUCUCACUAGUG	1195	21513	CACUAGUGAGAGUAAGAAA	2846
21513	GGUAGUGACCUUGACCGGU	1196	21513	GGUAGUGACCUUGACCGGU	1196	21531	ACCGGUCAAGGUCACUACC	2847
21531	UGCACCACUUUUGAUGAUG	1197	21531	UGCACCACUUUUGAUGAUG	1197	21549	CAUCAUCAAAAGUGGUGCA	2848
21549	GUUCAAGCUCCUAAUUACA	1198	21549	GUUCAAGCUCCUAAUUACA	1198	21567	UGUAAUUAGGAGCUUGAAC	2849
21567	ACUCAACAUACUUCAUCUA	1199	21567	ACUCAACAUACUUCAUCUA	1199	21585	UAGAUGAAGUAUGUUGAGU	2850
21585	AUGAGGGGGUUUACUAUC	1200	21585	AUGAGGGGGUUUACUAUC	1200	21603	GAUAGUAAACCCCCUCAU	2851
21603	CCUGAUGAAAUUUUUAGAU	1201	21603	CCUGAUGAAAUUUUUAGAU	1201	21621	AUCUAAAAAUUUCAUCAGG	2852
21621	UCAGACACUCUUUAUUUAA	1202	21621	UCAGACACUCUUUAUUUAA	1202	21639	UUAAAUAAAGAGUGUCUGA	2853
21639	ACUCAGGAUUUAUUUCUUC	1203	21639	ACUCAGGAUUUAUUUCUUC	1203	21657	GAAGAAAUAAAUCCUGAGU	2854
21657	CCAUUUUAUUCUAAUGUUA	1204	21657	CCAUUUUAUUCUAAUGUUA	1204	21675	UAACAUUAGAAUAAAAUGG	2855
21675	ACAGGGUUUCAUACUAUUA	1205	21675	ACAGGGUUUCAUACUAUUA	1205	21693	UAAUAGUAUGAAACCCUGU	2856
21693	AAUCAUACGUUUGGCAACC	1206	21693	AAUCAUACGUUUGGCAACC	1206	21711	GGUUGCCAAACGUAUGAUU	2857
21711	CCUGUCAUACCUUUUAAGG	1207	21711	CCUGUCAUACCUUUUAAGG	1207	21729	CCUUAAAAGGUAUGACAGG	2858
21729	GAUGGUAUUUAUUUUGCUG	1208	21729	GAUGGUAUUUAUUUUGCUG	1208	21747	CAGCAAAAUAAAUACCAUC	2859
21747	GCCACAGAGAAAUCAAAUG	1209	21747	GCCACAGAGAAAUCAAAUG	1209	21765	CAUUUGAUUUCUCUGUGGC	2860
21765	GUUGUCCGUGGUUGGGUUU	1210	21765	GUUGUCCGUGGUUGGGUUU	1210	21783	AAACCCAACCACGGACAAC	2861
21783	UUUGGUUCUACCAUGAACA	1211	21783	UUUGGUUCUACCAUGAACA	1211	21801	UGUUCAUGGUAGAACCAAA	2862
21801	AACAAGUCACAGUCGGUGA	1212	21801	AACAAGUCACAGUCGGUGA	1212	21819	UCACCGACUGUGACUUGUU	2863

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21819	AUUAUUAUUAACAAUUCUA	1213	21819	AUUAUUAUUAACAAUUCUA	1213	21837	UAGAAUUGUUAAUAAUAAU	2864
21837	ACUAAUGUUGUUAUACGAG	1214	21837	ACUAAUGUUGUUAUACGAG	1214	21855	CUCGUAUAACAACAUUAGU	2865
21855	GCAUGUAACUUUGAAUUGU	1215	21855	GCAUGUAACUUUGAAUUGU	1215	21873	ACAAUUCAAAGUUACAUGC	2866
21873	UGUGACAACCCUUUCUUUG	1216	21873	UGUGACAACCCUUUCUUUG	1216	21891	CAAAGAAAGGGUUGUCACA	2867
21891	GCUGUUUCUAAACCCAUGG	1217	21891	GCUGUUUCUAAACCCAUGG	1217	21909	CCAUGGGUUUAGAAACAGC	2868
21909	GGUACACAGACACAUACUA	1218	21909	GGUACACAGACACAUACUA	1218	21927	UAGUAUGUGUCUGUGUACC	2869
21927	AUGAUAUUCGAUAAUGCAU	1219	21927	AUGAUAUUCGAUAAUGCAU	1219	21945	AUGCAUUAUCGAAUAUCAU	2870
21945	UUUAAUUGCACUUUCGAGU	1220	21945	UUUAAUUGCACUUUCGAGU	1220	21963	ACUCGAAAGUGCAAUUAAA	2871
21963	UACAUAUCUGAUGCCUUUU	1221	21963	UACAUAUCUGAUGCCUUUU	1221	21981	AAAAGGCAUCAGAUAUGUA	2872
21981	UCGCUUGAUGUUUCAGAAA	1222	21981	UCGCUUGAUGUUUCAGAAA	1222	21999	UUUCUGAAACAUCAAGCGA	2873
21999	AAGUCAGGUAAUUUUAAAC	1223	21999	AAGUCAGGUAAUUUUAAAC	1223	22017	GUUUAAAAUUACCUGACUU	2874
22017	CACUUACGAGAGUUUGUGU	1224	22017	CACUUACGAGAGUUUGUGU	1224	22035	ACACAAACUCUCGUAAGUG	2875
22035	UUUAAAAAUAAAGAUGGGU	1225	22035	UUUAAAAAUAAAGAUGGGU	1225	22053	ACCCAUCUUUAUUUUUAAA	2876
22053	UUUCUCUAUGUUUAUAAGG	1226	22053	UUUCUCUAUGUUUAUAAGG	1226	22071	CCUUAUAAACAUAGAGAAA	2877
22071	GGCUAUCAACCUAUAGAUG	1227	22071	GGCUAUCAACCUAUAGAUG	1227	22089	CAUCUAUAGGUUGAUAGCC	2878
22089	GUAGUUCGUGAUCUACCUU	1228	22089	GUAGUUCGUGAUCUACCUU	1228	22107	AAGGUAGAUCACGAACUAC	2879
22107	UCUGGUUUUAACACUUUGA	1229	22107	UCUGGUUUUAACACUUUGA	1229	22125	UCAAAGUGUUAAAACCAGA	2880
22125	AAACCUAUUUUUAAGUUGC	1230	22125	AAACCUAUUUUUAAGUUGC	1230	22143	GCAACUUAAAAAUAGGUUU	2881
22143	CCUCUUGGUAUUAACAUUA	1231	22143	CCUCUUGGUAUUAACAUUA	1231	22161	UAAUGUUAAUACCAAGAGG	2882
22161	ACAAAUUUUAGAGCCAUUC	1232	22161	ACAAAUUUUAGAGCCAUUC	1232	22179	GAAUGGCUCUAAAAUUUGU	2883
22179	CUUACAGCCUUUUCACCUG	1233	22179	CUUACAGCCUUUUCACCUG	1233	22197	CAGGUGAAAAGGCUGUAAG	2884
22197	GCUCAAGACAUUUGGGGCA	1234	22197	GCUCAAGACAUUUGGGGCA	1234	22215	UGCCCCAAAUGUCUUGAGC	2885
22215	ACGUCAGCUGCAGCCUAUU	1235	22215	ACGUCAGCUGCAGCCUAUU	1235	22233	AAUAGGCUGCAGCUGACGU	2886
22233	UUUGUUGGCUAUUUAAAGC	1236	22233	UUUGUUGGCUAUUUAAAGC	1236	22251	GCUUUAAAUAGCCAACAAA	2887
22251	CCAACUACAUUUAUGCUCA	1237	22251	CCAACUACAUUUAUGCUCA	1237	22269	UGAGCAUAAAUGUAGUUGG	2888
22269	AAGUAUGAUGAAAAUGGUA	1238	22269	AAGUAUGAUGAAAAUGGUA	1238	22287	UACCAUUUUCAUCAUACUU	2889
22287	ACAAUCACAGAUGCUGUUG	1239	22287	ACAAUCACAGAUGCUGUUG	1239	22305	CAACAGCAUCUGUGAUUGU	2890
22305	GAUUGUUCUCAAAAUCCAC	1240	22305	GAUUGUUCUCAAAAUCCAC	1240	22323	GUGGAUUUUGAGAACAAUC	2891
22323	CUUGCUGAACUCAAAUGCU	1241	22323	CUUGCUGAACUCAAAUGCU	1241	22341	AGCAUUUGAGUUCAGCAAG	2892
22341	UCUGUUAAGAGCUUUGAGA	1242	22341	UCUGUUAAGAGCUUUGAGA	1242	22359	UCUCAAAGCUCUUAACAGA	2893
22359	AUUGACAAAGGAAUUUACC	1243	22359	AUUGACAAAGGAAUUUACC	1243	22377	GGUAAAUUCCUUUGUCAAU	2894
22377	CAGACCUCUAAUUUCAGGG	1244	22377	CAGACCUCUAAUUUCAGGG	1244	22395	CCCUGAAAUUAGAGGUCUG	2895
22395	GUUGUUCCCUCAGGAGAUG	1245	22395	GUUGUUCCCUCAGGAGAUG	1245	22413	CAUCUCCUGAGGGAACAAC	2896
22413	GUUGUGAGAUUCCCUAAUA	1246	22413	GUUGUGAGAUUCCCUAAUA	1246	22431	UAUUAGGGAAUCUCACAAC	2897
22431	AUUACAAACUUGUGUCCUU	1247	22431	AUUACAAACUUGUGUCCUU	1247	22449	AAGGACACAAGUUUGUAAU	2898
22449	UUUGGAGAGGUUUUUAAUG	1248	22449	UUUGGAGAGGUUUUUAAUG	1248	22467	CAUUAAAAACCUCUCCAAA	2899
22467	GCUACUAAAUUCCCUUCUG	1249	22467	GCUACUAAAUUCCCUUCUG	1249	22485	CAGAAGGGAAUUUAGUAGC	2900
22485	GUCUAUGCAUGGGAGAGAA	1250	22485	GUCUAUGCAUGGGAGAGAA	1250	22503	UUCUCUCCCAUGCAUAGAC	2901
22503	AAAAAAAUUUCUAAUUGUG	1251	22503	AAAAAAAUUUCUAAUUGUG	1251	22521	CACAAUUAGAAAUUUUUUU	2902
22521	GUUGCUGAUUACUCUGUGC	1252	22521	GUUGCUGAUUACUCUGUGC	1252	22539	GCACAGAGUAAUCAGCAAC	2903
22539	CUCUACAACUCAACAUUUU	1253	22539	CUCUACAACUCAACAUUUU	1253	22557	AAAAUGUUGAGUUGUAGAG	2904
22557	UUUUCAACCUUUAAGUGCU	1254	22557	UUUUCAACCUUUAAGUGCU	1254	22575	AGCACUUAAAGGUUGAAAA	2905

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22575	UAUGGCGUUUCUGCCACUA	1255	22575	UAUGGCGUUUCUGCCACUA	1255	22593	UAGUGGCAGAAACGCCAUA	2906
22593	AAGUUGAAUGAUCUUUGCU	1256	22593	AAGUUGAAUGAUCUUUGCU	1256	22611	AGCAAAGAUCAUUCAACUU	2907
22611	UUCUCCAAUGUCUAUGCAG	1257	22611	UUCUCCAAUGUCUAUGCAG	1257	22629	CUGCAUAGACAUUGGAGAA	2908
22629	GAUUCUUUUGUAGUCAAGG	1258	22629	GAUUCUUUUGUAGUCAAGG	1258	22647	CCUUGACUACAAAAGAAUC	2909
22647	GGAGAUGAUGUAAGACAAA	1259	22647	GGAGAUGAUGUAAGACAAA	1259	22665	UUUGUCUUACAUCAUCUCC	2910
22665	AUAGCGCCAGGACAAACUG	1260	22665	AUAGCGCCAGGACAAACUG	1260	22683	CAGUUUGUCCUGGCGCUAU	2911
22683	GGUGUUAUUGCUGAUUAUA	1261	22683	GGUGUUAUUGCUGAUUAUA	1261	22701	UAUAAUCAGCAAUAACACC	2912
22701	AAUUAUAAAUUGCCAGAUG	1262	22701	AAUUAUAAAUUGCCAGAUG	1262	22719	CAUCUGGCAAUUUAUAAUU	2913
22719	GAUUUCAUGGGUUGUGUCC	1263	22719	GAUUUCAUGGGUUGUGUCC	1263	22737	GGACACAACCCAUGAAAUC	2914
22737	CUUGCUUGGAAUACUAGGA	1264	22737	CUUGCUUGGAAUACUAGGA	1264	22755	UCCUAGUAUUCCAAGCAAG	2915
22755	AACAUUGAUGCUACUUCAA	1265	22755	AACAUUGAUGCUACUUCAA	1265	22773	UUGAAGUAGCAUCAAUGUU	2916
22773	ACUGGUAAUUAUAAUUAUA	1266	22773	ACUGGUAAUUAUAAUUAUA	1266	22791	UAUAAUUAUAAUUACCAGU	2917
22791	AAAUAUAGGUAUCUUAGAC	1267	22791	AAAUAUAGGUAUCUUAGAC	1267	22809	GUCUAAGAUACCUAUAUUU	2918
22809	CAUGGCAAGCUUAGGCCCU	1268	22809	CAUGGCAAGCUUAGGCCCU	1268	22827	AGGGCCUAAGCUUGCCAUG	2919
22827	UUUGAGAGAGACAUAUCUA	1269	22827	UUUGAGAGAGACAUAUCUA	1269	22845	UAGAUAUGUCUCUCUCAAA	2920
22845	AAUGUGCCUUUCUCCCCUG	1270	22845	AAUGUGCCUUUCUCCCCUG	1270	22863	CAGGGGAGAAAGGCACAUU	2921
22863	GAUGGCAAACCUUGCACCC	1271	22863	GAUGGCAAACCUUGCACCC	1271	22881	GGGUGCAAGGUUUGCCAUC	2922
22881	CCACCUGCUCUUAAUUGUU	1272	22881	CCACCUGCUCUUAAUUGUU	1272	22899	AACAAUUAAGAGCAGGUGG	2923
22899	UAUUGGCCAUUAAAUGAUU	1273	22899	UAUUGGCCAUUAAAUGAUU	1273	22917	AAUCAUUUAAUGGCCAAUA	2924
22917	UAUGGUUUUUACACCACUA	1274	22917	UAUGGUUUUUACACCACUA	1274	22935	UAGUGGUGUAAAAACCAUA	2925
22935	ACUGGCAUUGGCUACCAAC	1275	22935	ACUGGCAUUGGCUACCAAC	1275	22953	GUUGGUAGCCAAUGCCAGU	2926
22953	CCUUACAGAGUUGUAGUAC	1276	22953	CCUUACAGAGUUGUAGUAC	1276	22971	GUACUACAACUCUGUAAGG	2927
22971	CUUUCUUUUGAACUUUUAA	1277	22971	CUUUCUUUUGAACUUUUAA	1277	22989	UUAAAAGUUCAAAAGAAAG	2928
22989	AAUGCACCGGCCACGGUUU	1278	22989	AAUGCACCGGCCACGGUUU	1278	23007	AAACCGUGGCCGGUGCAUU	2929
23007	UGUGGACCAAAAUUAUCCA	1279	23007	UGUGGACCAAAAUUAUCCA	1279	23025	UGGAUAAUUUUGGUCCACA	2930
23025	ACUGACCUUAUUAAGAACC	1280	23025	ACUGACCUUAUUAAGAACC	1280	23043	GGUUCUUAAUAAGGUCAGU	2931
23043	CAGUGUGUCAAUUUUAAUU	1281	23043	CAGUGUGUCAAUUUUAAUU	1281	23061	AAUUAAAAUUGACACACUG	2932
23061	UUUAAUGGACUCACUGGUA	1282	23061	UUUAAUGGACUCACUGGUA	1282	23079	UACCAGUGAGUCCAUUAAA	2933
23079	ACUGGUGUGUUAACUCCUU	1283	23079	ACUGGUGUGUUAACUCCUU	1283	23097	AAGGAGUUAACACACCAGU	2934
23097	UCUUCAAAGAGAUUUCAAC	1284	23097	UCUUCAAAGAGAUUUCAAC	1284	23115	GUUGAAAUCUCUUUGAAGA	2935
23115	CCAUUUCAACAAUUUGGCC	1285	23115	CCAUUUCAACAAUUUGGCC	1285	23133	GGCCAAAUUGUUGAAAUGG	2936
23133	CGUGAUGUUUCUGAUUUCA	1286	23133	CGUGAUGUUUCUGAUUUCA	1286	23151	UGAAAUCAGAAACAUCACG	2937
23151	ACUGAUUCCGUUCGAGAUC	1287	23151	ACUGAUUCCGUUCGAGAUC	1287	23169	GAUCUCGAACGGAAUCAGU	2938
23169	CCUAAAACAUCUGAAAUAU	1288	23169	CCUAAAACAUCUGAAAUAU	1288	23187	AUAUUUCAGAUGUUUUAGG	2939
23187	UUAGACAUUUCACCUUGCG	1289	23187	UUAGACAUUUCACCUUGCG	1289	23205	CGCAAGGUGAAAUGUCUAA	2940
23205	GCUUUUGGGGGUGUAAGUG	1290	23205	GCUUUUGGGGGUGUAAGUG	1290	23223	CACUUACACCCCCAAAAGC	2941
23223	GUAAUUACACCUGGAACAA	1291	23223	GUAAUUACACCUGGAACAA	1291	23241	UUGUUCCAGGUGUAAUUAC	2942
23241	AAUGCUUCAUCUGAAGUUG	1292	23241	AAUGCUUCAUCUGAAGUUG	1292	23259	CAACUUCAGAUGAAGCAUU	2943
23259	GCUGUUCUAUAUCAAGAUG	1293	23259	GCUGUUCUAUAUCAAGAUG	1293	23277	CAUCUUGAUAUAGAACAGC	2944
23277	GUUAACUGCACUGAUGUUU	1294	23277	GUUAACUGCACUGAUGUUU	1294	23295	AAACAUCAGUGCAGUUAAC	2945
23295	UCUACAGCAAUUCAUGCAG	1295	23295	UCUACAGCAAUUCAUGCAG	1205	23313	CUGCAUGAAUUGCUGUAGA	2946
23313	GAUCAACUCACACCAGCUU	1296	23313	GAUCAACUCACACCAGCUU	1296	23331	AAGCUGGUGUGAGUUGAUC	2947

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23331	UGGCGCAUAUAUUCUACUG	1297	23331	UGGCGCAUAUAUUCUACUG	1297	23349	CAGUAGAAUAUAUGCGCCA	2948
23349	GGAAACAAUGUAUUCCAGA	1298	23349	GGAAACAAUGUAUUCCAGA	1298	23367	UCUGGAAUACAUUGUUUCC	2949
23367	ACUCAAGCAGGCUGUCUUA	1299	23367	ACUCAAGCAGGCUGUCUUA	1299	23385	UAAGACAGCCUGCUUGAGU	2950
23385	AUAGGAGCUGAGCAUGUCG	1300	23385	AUAGGAGCUGAGCAUGUCG	1300	23403	CGACAUGCUCAGCUCCUAU	2951
23403	GACACUUCUUAUGAGUGCG	1301	23403	GACACUUCUUAUGAGUGCG	1301	23421	CGCACUCAUAAGAAGUGUC	2952
23421	GACAUUCCUAUUGGAGCUG	1302	23421	GACAUUCCUAUUGGAGCUG	1302	23439	CAGCUCCAAUAGGAAUGUC	2953
23439	GGCAUUUGUGCUAGUUACC	1303	23439	GGCAUUUGUGCUAGUUACC	1303	23457	GGUAACUAGCACAAAUGCC	2954
23457	CAUACAGUUUCUUUAUUAC	1304	23457	CAUACAGUUUCUUUAUUAC	1304	23475	GUAAUAAAGAAACUGUAUG	2955
23475	CGUAGUACUAGCCAAAAAU	1305	23475	CGUAGUACUAGCCAAAAAU	1305	23493	AUUUUUGGCUAGUACUACG	2956
23493	UCUAUUGUGGCUUAUACUA	1306	23493	UCUAUUGUGGCUUAUACUA	1306	23511	UAGUAUAAGCCACAAUAGA	2957
23511	AUGUCUUUAGGUGCUGAUA	1307	23511	AUGUCUUUAGGUGCUGAUA	1307	23529	UAUCAGCACCUAAAGACAU	2958
23529	AGUUCAAUUGCUUACUCUA	1308	23529	AGUUCAAUUGCUUACUCUA	1308	23547	UAGAGUAAGCAAUUGAACU	2959
23547	AAUAACACCAUUGCUAUAC	1309	23547	AAUAACACCAUUGCUAUAC	1309	23565	GUAUAGCAAUGGUGUUAUU	2960
23565	CCUACUAACUUUUCAAUUA	1310	23565	CCUACUAACUUUUCAAUUA	1310	23583	UAAUUGAAAAGUUAGUAGG	2961
23583	AGCAUUACUACAGAAGUAA	1311	23583	AGCAUUACUACAGAAGUAA	1311	23601	UUACUUCUGUAGUAAUGCU	2962
23601	AUGCCUGUUUCUAUGGCUA	1312	23601	AUGCCUGUUUCUAUGGCUA	1312	23619	UAGCCAUAGAAACAGGCAU	2963
23619	AAAACCUCCGUAGAUUGUA	1313	23619	AAAACCUCCGUAGAUUGUA	1313	23637	UACAAUCUACGGAGGUUUU	2964
23637	AAUAUGUACAUCUGCGGAG	1314	23637	AAUAUGUACAUCUGCGGAG	1314	23655	CUCCGCAGAUGUACAUAUU	2965
23655	GAUUCUACUGAAUGUGCUA	1315	23655	GAUUCUACUGAAUGUGCUA	1315	23673	UAGCACAUUCAGUAGAAUC	2966
23673	AAUUUGCUUCUCCAAUAUG	1316	23673	AAUUUGCUUCUCCAAUAUG	1316	23691	CAUAUUGGAGAAGCAAAUU	2967
23691	GGUAGCUUUUGCACACAAC	1317	23691	GGUAGCUUUUGCACACAAC	1317	23709	GUUGUGUGCAAAAGCUACC	2968
23709	CUAAAUCGUGCACUCUCAG	1318	23709	CUAAAUCGUGCACUCUCAG	1318	23727	CUGAGAGUGCACGAUUUAG	2969
23727	GGUAUUGCUGCUGAACAGG	1319	23727	GGUAUUGCUGCUGAACAGG	1319	23745	CCUGUUCAGCAGCAAUACC	2970
23745	GAUCGCAACACACGUGAAG	1320	23745	GAUCGCAACACACGUGAAG	1320	23763	CUUCACGUGUGUUGCGAUC	2971
23763	GUGUUCGCUCAAGUCAAAC	1321	23763	GUGUUCGCUCAAGUCAAAC	1321	23781	GUUUGACUUGAGCGAACAC	2972
23781	CAAAUGUACAAAACCCCAA	1322	23781	CAAAUGUACAAAACCCCAA	1322	23799	UUGGGGUUUUGUACAUUUG	2973
23799	ACUUUGAAAUAUUUUGGUG	1323	23799	ACUUUGAAAUAUUUUGGUG	1323	23817	CACCAAAAUAUUUCAAAGU	2974
23817	GGUUUUAAUUUUUCACAAA	1324	23817	GGUUUUAAUUUUUCACAAA	1324	23835	UUUGUGAAAAAUUAAAACC	2975
23835	AUAUUACCUGACCCUCUAA	1325	23835	AUAUUACCUGACCCUCUAA	1325	23853	UUAGAGGGUCAGGUAAUAU	2976
23853	AAGCCAACUAAGAGGUCUU	1326	23853	AAGCCAACUAAGAGGUCUU	1326	23871	AAGACCUCUUAGUUGGCUU	2977
23871	UUUAUUGAGGACUUGCUCU	1327	23871	UUUAUUGAGGACUUGCUCU	1327	23889	AGAGCAAGUCCUCAAUAAA	2978
23889	UUUAAUAAGGUGACACUCG	1328	23889	UUUAAUAAGGUGACACUCG	1328	23907	CGAGUGUCACCUUAUUAAA	2979
23907	GCUGAUGCUGGCUUCAUGA	1329	23907	GCUGAUGCUGGCUUCAUGA	1329	23925	UCAUGAAGCCAGCAUCAGC	2980
23925	AAGCAAUAUGGCGAAUGCC	1330	23925	AAGCAAUAUGGCGAAUGCC	1330	23943	GGCAUUCGCCAUAUUGCUU	2981
23943	CUAGGUGAUAUUAAUGCUA	1331	23943	CUAGGUGAUAUUAAUGCUA	1331	23961	UAGCAUUAAUAUCACCUAG	2982
23961	AGAGAUCUCAUUUGUGCGC	1332	23961	AGAGAUCUCAUUUGUGCGC	1332	23979	GCGCACAAAUGAGAUCUCU	2983
23979	CAGAAGUUCAAUGGACUUA	1333	23979	CAGAAGUUCAAUGGACUUA	1333	23997	UAAGUCCAUUGAACUUCUG	2984
23997	ACAGUGUUGCCACCUCUGC	1334	23997	ACAGUGUUGCCACCUCUGC	1334	24015	GCAGAGGUGGCAACACUGU	2985
24015	CUCACUGAUGAUAUGAUUG	1335	24015	CUCACUGAUGAUAUGAUUG	1335	24033	CAAUCAUAUCAUCAGUGAG	2986
24033	GCUGCCUACACUGCUGCUC	1336	24033	GCUGCCUACACUGCUGCUC	1336	24051	GAGCAGCAGUGUAGGCAGC	2987
24051	CUAGUUAGUGGUACUGCCA	1337	24051	CUAGUUAGUGGUACUGCCA	1337	24069	UGGCAGUACCACUAACUAG	2988
24069	ACUGCUGGAUGGACAUUUG	1338	24069	ACUGCUGGAUGGACAUUUG	1338	24087	CAAAUGUCCAUCCAGCAGU	2989

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24087	GGUGCUGGCGCUGCUCUUC	1339	24087	GGUGCUGGCGCUGCUCUUC	1339	24105	GAAGAGCAGCGCCAGCACC	2990
24105	CAAAUACCUUUUGCUAUGC	1340	24105	CAAAUACCUUUUGCUAUGC	1340	24123	GCAUAGCAAAAGGUAUUUG	2991
24123	CAAAUGGCAUAUAGGUUCA	1341	24123	CAAAUGGCAUAUAGGUUCA	1341	24141	UGAACCUAUAUGCCAUUUG	2992
24141	AAUGGCAUUGGAGUUACCC	1342	24141	AAUGGCAUUGGAGUUACCC	1342	24159	GGGUAACUCCAAUGCCAUU	2993
24159	CAAAAUGUUCUCUAUGAGA	1343	24159	CAAAAUGUUCUCUAUGAGA	1343	24177	UCUCAUAGAGAACAUUUUG	2994
24177	AACCAAAAACAAAUCGCCA	1344	24177	AACCAAAAACAAAUCGCCA	1344	24195	UGGCGAUUUGUUUUUGGUU	2995
24195	AACCAAUUUAACAAGGCGA	1345	24195	AACCAAUUUAACAAGGCGA	1345	24213	UCGCCUUGUUAAAUUGGUU	2996
24213	AUUAGUCAAAUUCAAGAAU	1346	24213	AUUAGUCAAAUUCAAGAAU	1346	24231	AUUCUUGAAUUUGACUAAU	2997
24231	UCACUUACAACAACAUCAA	1347	24231	UCACUUACAACAACAUCAA	1347	24249	UUGAUGUUGUUGUAAGUGA	2998
24249	ACUGCAUUGGGCAAGCUGC	1348	24249	ACUGCAUUGGGCAAGCUGC	1348	24267	GCAGCUUGCCCAAUGCAGU	2999
24267	CAAGACGUUGUUAACCAGA	1349	24267	CAAGACGUUGUUAACCAGA	1349	24285	UCUGGUUAACAACGUCUUG	3000
24285	AAUGCUCAAGCAUUAAACA	1350	24285	AAUGCUCAAGCAUUAAACA	1350	24303	UGUUUAAUGCUUGAGCAUU	3001
24303	ACACUUGUUAAACAACUUA	1351	24303	ACACUUGUUAAACAACUUA	1351	24321	UAAGUUGUUUAACAAGUGU	3002
24321	AGCUCUAAUUUUGGUGCAA	1352	24321	AGCUCUAAUUUUGGUGCAA	1352	24339	UUGCACCAAAAUUAGAGCU	3003
24339	AUUUCAAGUGUGCUAAAUG	1353	24339	AUUUCAAGUGUGCUAAAUG	1353	24357	CAUUUAGCACACUUGAAAU	3004
24357	GAUAUCCUUUCGCGACUUG	1354	24357	GAUAUCCUUUCGCGACUUG	1354	24375	CAAGUCGCGAAAGGAUAUC	3005
24375	GAUAAAGUCGAGGCGGAGG	1355	24375	GAUAAAGUCGAGGCGGAGG	1355	24393	CCUCCGCCUCGACUUUAUC	3006
24393	GUACAAAUUGACAGGUUAA	1356	24393	GUACAAAUUGACAGGUUAA	1356	24411	UUAACCUGUCAAUUUGUAC	3007
24411	AUUACAGGCAGACUUCAAA	1357	24411	AUUACAGGCAGACUUCAAA	1357	24429	UUUGAAGUCUGCCUGUAAU	3008
24429	AGCCUUCAAACCUAUGUAA	1358	24429	AGCCUUCAAACCUAUGUAA	1358	24447	UUACAUAGGUUUGAAGGCU	3009
24447	ACACAACAACUAAUCAGGG	1359	24447	ACACAACAACUAAUCAGGG	1359	24465	CCCUGAUUAGUUGUUGUGU	3010
24465	GCUGCUGAAAUCAGGGCUU	1360	24465	GCUGCUGAAAUCAGGGCUU	1360	24483	AAGCCCUGAUUUCAGCAGC	3011
24483	UCUGCUAAUCUUGCUGCUA	1361	24483	UCUGCUAAUCUUGCUGCUA	1361	24501	UAGCAGCAAGAUUAGCAGA	3012
24501	ACUAAAAUGUCUGAGUGUG	1362	24501	ACUAAAAUGUCUGAGUGUG	1362	24519	CACACUCAGACAUUUUAGU	3013
24519	GUUCUUGGACAAUCAAAAA	1363	24519	GUUCUUGGACAAUCAAAAA	1363	24537	UUUUUGAUUGUCCAAGAAC	3014
24537	AGAGUUGACUUUUGUGGAA	1364	24537	AGAGUUGACUUUUGUGGAA	1364	24555	UUCCACAAAAGUCAACUCU	3015
24555	AAGGGCUACCACCUUAUGU	1365	24555	AAGGGCUACCACCUUAUGU	1365	24573	ACAUAAGGUGGUAGCCCUU	3016
24573	UCCUUCCCACAAGCAGCCC	1366	24573	UCCUUCCCACAAGCAGCCC	1366	24591	GGGCUGCUUGUGGGAAGGA	3017
24591	CCGCAUGGUGUUGUCUUCC	1367	24591	CCGCAUGGUGUUGUCUUCC	1367	24609	GGAAGACAACACCAUGCGG	3018
24609	CUACAUGUCACGUAUGUGC	1368	24609	CUACAUGUCACGUAUGUGC	1368	24627	GCACAUACGUGACAUGUAG	3019
24627	CCAUCCCAGGAGAGGAACU	1369	24627	CCAUCCCAGGAGAGGAACU	1369	24645	AGUUCCUCUCCUGGGAUGG	3020
24645	UUCACCACAGCGCCAGCAA	1370	24645	UUCACCACAGCGCCAGCAA	1370	24663	UUGCUGGCGCUGUGGUGAA	3021
24663	AUUUGUCAUGAAGGCAAAG	1371	24663	AUUUGUCAUGAAGGCAAAG	1371	24681	CUUUGCCUUCAUGACAAAU	3022
24681	GCAUACUUCCCUCGUGAAG	1372	24681	GCAUACUUCCCUCGUGAAG	1372	24699	CUUCACGAGGGAAGUAUGC	3023
24699	GGUGUUUUUGUGUUUAAUG	1373	24699	GGUGUUUUUGUGUUUAAUG	1373	24717	CAUUAAACACAAAAACACC	3024
24717	GGCACUUCUUGGUUUAUUA	1374	24717	GGCACUUCUUGGUUUAUUA	1374	24735	UAAUAAACCAAGAAGUGCC	3025
24735	ACACAGAGGAACUUCUUUU	1375	24735	ACACAGAGGAACUUCUUUU	1375	24753	AAAAGAAGUUCCUCUGUGU	3026
24753	UCUCCACAAAUAAUUACUA	1376	24753	UCUCCACAAAUAAUUACUA	1376	24771	UAGUAAUUAUUUGUGGAGA	3027
24771	ACAGACAAUACAUUUGUCU	1377	24771	ACAGACAAUACAUUUGUCU	1377	24789	AGACAAAUGUAUUGUCUGU	3028
24789	UCAGGAAAUUGUGAUGUCG	1378	24789	UCAGGAAAUUGUGAUGUCG	1378	24807	CGACAUCACAAUUUCCUGA	3029
24807	GUUAUUGGCAUCAUUAACA	1379	24807	GUUAUUGGCAUCAUUAACA	1379	24825	UGUUAAUGAUGCCAAUAAC	3030
24825	AACACAGUUUAUGAUCCUC	1380	24825	AACACAGUUUAUGAUCCUC	1380	24843	GAGGAUCAUAAACUGUGUU	3031

24843	CUGCAACCUGAGCUUGACU	1381	24843	CUGCAACCUGAGCUUGACU	1381	24861	AGUCAAGCUCAGGUUGCAG	3032
24861	UCAUUCAAAGAAGAGCUGG	1382	24861	UCAUUCAAAGAAGAGCUGG	1382	24879	CCAGCUCUUCUUUGAAUGA	3033
24879	GACAAGUACUUCAAAAAUC	1383	24879	GACAAGUACUUCAAAAAUC	1383	24897	GAUUUUUGAAGUACUUGUC	3034
24897	CAUACAUCACCAGAUGUUG	1384	24897	CAUACAUCACCAGAUGUUG	1384	24915	CAACAUCUGGUGAUGUAUG	3035
24915	GAUCUUGGCGACAUUUCAG	1385	24915	GAUCUUGGCGACAUUUCAG	1385	24933	CUGAAAUGUCGCCAAGAUC	3036
24933	GGCAUUAACGCUUCUGUCG	1386	24933	GGCAUUAACGCUUCUGUCG	1386	24951	CGACAGAAGCGUUAAUGCC	3037
24951	GUCAACAUUCAAAAAGAAA	1387	24951	GUCAACAUUCAAAAAGAAA	1387	24969	UUUCUUUUUGAAUGUUGAC	3038
24969	AUUGACCGCCUCAAUGAGG	1388	24969	AUUGACCGCCUCAAUGAGG	1388	24987	CCUCAUUGAGGCGGUCAAU	3039
24987	GUCGCUAAAAAUUUAAAUG	1389	24987	GUCGCUAAAAAUUUAAAUG	1389	25005	CAUUUAAAUUUUUAGCGAC	3040
25005	GAAUCACUCAUUGACCUUC	1390	25005	GAAUCACUCAUUGACCUUC	1390	25023	GAAGGUCAAUGAGUGAUUC	3041
25023	CAAGAAUUGGGAAAAUAUG	1391	25023	CAAGAAUUGGGAAAAUAUG	1391	25041	CAUAUUUUCCCAAUUCUUG	3042
25041	GAGCAAUAUAUUAAAUGGC	1392	25041	GAGCAAUAUAUUAAAUGGC	1392	25059	GCCAUUUAAUAUAUUGCUC	3043
25059	CCUUGGUAUGUUUGGCUCG	1393	25059	CCUUGGUAUGUUUGGCUCG	1393	25077	CGAGCCAAACAUACCAAGG	3044
25077	GGCUUCAUUGCUGGACUAA	1394	25077	GGCUUCAUUGCUGGACUAA	1394	25095	UUAGUCCAGCAAUGAAGCC	3045
25095	AUUGCCAUCGUCAUGGUUA	1395	25095	AUUGCCAUCGUCAUGGUUA	1395	25113	UAACCAUGACGAUGGCAAU	3046
25113	ACAAUCUUGCUUUGUUGCA	1396	25113	ACAAUCUUGCUUUGUUGCA	1396	25131	UGCAACAAAGCAAGAUUGU	3047
25131	AUGACUAGUUGUUGCAGUU	1397	25131	AUGACUAGUUGUUGCAGUU	1397	25149	AACUGCAACAACUAGUCAU	3048
25149	UGCCUCAAGGGUGCAUGCU	1398	25149	UGCCUCAAGGGUGCAUGCU	1398	25167	AGCAUGCACCCUUGAGGCA	3049
25167	UCUUGUGGUUCUUGCUGCA	1399	25167	UCUUGUGGUUCUUGCUGCA	1399	25185	UGCAGCAAGAACCACAAGA	3050
25185	AAGUUUGAUGAGGAUGACU	1400	25185	AAGUUUGAUGAGGAUGACU	1400	25203	AGUCAUCCUCAUCAAACUU	3051
25203	UCUGAGCCAGUUCUCAAGG	1401	25203	UCUGAGCCAGUUCUCAAGG	1401	25221	CCUUGAGAACUGGCUCAGA	3052
25221	GGUGUCAAAUUACAUUACA	1402	25221	GGUGUCAAAUUACAUUACA	1402	25239	UGUAAUGUAAUUUGACACC	3053
25239	ACAUAAACGAACUUAUGGA	1403	25239	ACAUAAACGAACUUAUGGA	1403	25257	UCCAUAAGUUCGUUUAUGU	3054
25257	AUUUGUUUAUGAGAUUUUU	1404	25257	AUUUGUUUAUGAGAUUUUU	1404	25275	AAAAAUCUCAUAAACAAAU	3055
25275	UUACUCUUGGAUCAAUUAC	1405	25275	UUACUCUUGGAUCAAUUAC	1405	25293	GUAAUUGAUCCAAGAGUAA	3056
25293	CUGCACAGCCAGUAAAAAU	1406	25293	CUGCACAGCCAGUAAAAAU	1406	25311	AUUUUUACUGGCUGUGCAG	3057
25311	UUGACAAUGCUUCUCCUGC	1407	25311	UUGACAAUGCUUCUCCUGC	1407	25329	GCAGGAGAAGCAUUGUCAA	3058
25329	CAAGUACUGUUCAUGCUAC	1408	25329	CAAGUACUGUUCAUGCUAC	1408	25347	GUAGCAUGAACAGUACUUG	3059
25347	CAGCAACGAUACCGCUACA	1409	25347	CAGCAACGAUACCGCUACA	1409	25365	UGUAGCGGUAUCGUUGCUG	3060
25365	AAGCCUCACUCCCUUUCGG	1410	25365	AAGCCUCACUCCCUUUCGG	1410	25383	CCGAAAGGGAGUGAGGCUU	3061
25383	GAUGGCUUGUUAUUGGCGU	1411	25383	GAUGGCUUGUUAUUGGCGU	1411	25401	ACGCCAAUAACAAGCCAUC	3062
25401	UUGCAUUUCUUGCUGUUUU	1412	25401	UUGCAUUUCUUGCUGUUUU	1412	25419	AAAACAGCAAGAAAUGCAA	3063
25419	UUCAGAGCGCUACCAAAAU	1413	25419	UUCAGAGCGCUACCAAAAU	1413	25437	AUUUUGGUAGCGCUCUGAA	3064
25437	UAAUUGCGCUCAAUAAAAG	1414	25437	UAAUUGCGCUCAAUAAAAG	1414	25455	CUUUUAUUGAGCGCAAUUA	3065
25455	GAUGGCAGCUAGCCCUUUA	1415	25455	GAUGGCAGCUAGCCCUUUA	1415	25473	UAAAGGGCUAGCUGCCAUC	3066
25473	AUAAGGGCUUCCAGUUCAU	1416	25473	AUAAGGGCUUCCAGUUCAU	1416	25491	AUGAACUGGAAGCCCUUAU	3067
25491	UUUGCAAUUUACUGCUGCU	1417	25491	UUUGCAAUUUACUGCUGCU	1417	25509	AGCAGCAGUAAAUUGCAAA	3068
25509	UAUUUGUUACCAUCUAUUC	1418	25509	UAUUUGUUACCAUCUAUUC	1418	25527	GAAUAGAUGGUAACAAAUA	3069
25527	CACAUCUUUUGCUUGUCGC	1419	25527	CACAUCUUUUGCUUGUCGC	1419	25545	GCGACAAGCAAAAGAUGUG	3070
25545	CUGCAGGUAUGGAGGCGCA	1420	25545	CUGCAGGUAUGGAGGCGCA	1420	25563	UGCGCCUCCAUACCUGCAG	3071
25563	AAUUUUUGUACCUCUAUGC	1421	25563	AAUUUUUGUACCUCUAUGC	1421	25581	GCAUAGAGGUACAAAAAUU	3072
25581	CCUUGAUAUAUUUUCUACA	1422	25581	CCUUGAUAUAUUUUCUACA	1422	25599	UGUAGAAAAUAUAUCAAGG	3073

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25599	AAUGCAUCAACGCAUGUAG	1423	25599	AAUGCAUCAACGCAUGUAG	1423	25617	CUACAUGCGUUGAUGCAUU	3074
25617	GAAUUAUUAUGAGAUGUUG	1424	25617	GAAUUAUUAUGAGAUGUUG	1424	25635	CAACAUCUCAUAAUAAUUC	3075
25635	GGCUUUGUUGGAAGUGCAA	1425	25635	GGCUUUGUUGGAAGUGCAA	1425	25653	UUGCACUUCCAACAAAGCC	3076
25653	AAUCCAAGAACCCAUUACU	1426	25653	AAUCCAAGAACCCAUUACU	1426	25671	AGUAAUGGGUUCUUGGAUU	3077
25671	UUUAUGAUGCCAACUACUU	1427	25671	UUUAUGAUGCCAACUACUU	1427	25689	AAGUAGUUGGCAUCAUAAA	3078
25689	UUGUUUGCUGGCACACACA	1428	25689	UUGUUUGCUGGCACACACA	1428	25707	UGUGUGUGCCAGCAAACAA	3079
25707	AUAACUAUGACUACUGUAU	1429	25707	AUAACUAUGACUACUGUAU	1429	25725	AUACAGUAGUCAUAGUUAU	3080
25725	UACCAUAUAACAGUGUCAC	1430	25725	UACCAUAUAACAGUGUCAC	1430	25743	GUGACACUGUUAUAUGGUA	3081
25743	CAGAUACAAUUGUCGUUAC	1431	25743	CAGAUACAAUUGUCGUUAC	1431	25761	GUAACGACAAUUGUAUCUG	3082
25761	CUGAAGGUGACGGCAUUUC	1432	25761	CUGAAGGUGACGGCAUUUC	1432	25779	GAAAUGCCGUCACCUUCAG	3083
25779	CAACACCAAAACUCAAAGA	1433	25779	CAACACCAAAACUCAAAGA	1433	25797	UCUUUGAGUUUUGGUGUUG	3084
25797	AAGACUACCAAAUUGGUGG	1434	25797	AAGACUACCAAAUUGGUGG	1434	25815	CCACCAAUUUGGUAGUCUU	3085
25815	GUUAUUCUGAGGAUAGGCA	1435	25815	GUUAUUCUGAGGAUAGGCA	1435	25833	UGCCUAUCCUCAGAAUAAC	3086
25833	ACUCAGGUGUUAAAGACUA	1436	25833	ACUCAGGUGUUAAAGACUA	1436	25851	UAGUCUUUAACACCUGAGU	3087
25851	AUGUCGUUGUACAUGGCUA	1437	25851	AUGUCGUUGUACAUGGCUA	1437	25869	UAGCCAUGUACAACGACAU	3088
25869	AUUUCACCGAAGUUUACUA	1438	25869	AUUUCACCGAAGUUUACUA	1438	25887	UAGUAAACUUCGGUGAAAU	3089
25887	ACCAGCUUGAGUCUACACA	1439	25887	ACCAGCUUGAGUCUACACA	1439	25905	UGUGUAGACUCAAGCUGGU	3090
25905	AAAUUACUACAGACACUGG	1440	25905	AAAUUACUACAGACACUGG	1440	25923	CCAGUGUCUGUAGUAAUUU	3091
25923	GUAUUGAAAAUGCUACAUU	1441	25923	GUAUUGAAAAUGCUACAUU	1441	25941	AAUGUAGCAUUUUCAAUAC	3092
25941	UCUUCAUCUUUAACAAGCU	1442	25941	UCUUCAUCUUUAACAAGCU	1442	25959	AGCUUGUUAAAGAUGAAGA	3093
25959	UUGUUAAAGACCCACCGAA	1443	25959	UUGUUAAAGACCCACCGAA	1443	25977	UUCGGUGGGUCUUUAACAA	3094
25977	AUGUGCAAAUACACACAAU	1444	25977	AUGUGCAAAUACACACAAU	1444	25995	AUUGUGUGUAUUUGCACAU	3095
25995	UCGACGGCUCUUCAGGAGU	1445	25995	UCGACGGCUCUUCAGGAGU	1445	26013	ACUCCUGAAGAGCCGUCGA	3096
26013	UUGCUAAUCCAGCAAUGGA	1446	26013	UUGCUAAUCCAGCAAUGGA	1446	26031	UCCAUUGCUGGAUUAGCAA	3097
26031	AUCCAAUUUAUGAUGAGCC	1447	26031	AUCCAAUUUAUGAUGAGCC	1447	26049	GGCUCAUCAUAAAUUGGAU	3098
26049	CGACGACGACUACUAGCGU	1448	26049	CGACGACGACUACUAGCGU	1448	26067	ACGCUAGUAGUCGUCGUCG	3099
26067	UGCCUUUGUAAGCACAAGA	1449	26067	UGCCUUUGUAAGCACAAGA	1449	26085	UCUUGUGCUUACAAAGGCA	3100
26085	AAAGUGAGUACGAACUUAU	1450	26085	AAAGUGAGUACGAACUUAU	1450	26103	AUAAGUUCGUACUCACUUU	3101
26103	UGUACUCAUUCGUUUCGGA	1451	26103	UGUACUCAUUCGUUUCGGA	1451	26121	UCCGAAACGAAUGAGUACA	3102
26121	AAGAAACAGGUACGUUAAU	1452	26121	AAGAAACAGGUACGUUAAU	1452	26139	AUUAACGUACCUGUUUCUU	3103
26139	UAGUUAAUAGCGUACUUCU	1453	26139	UAGUUAAUAGCGUACUUCU	1453	26157	AGAAGUACGCUAUUAACUA	3104
26157	UUUUUCUUGCUUUCGUGGU	1454	26157	UUUUUCUUGCUUUCGUGGU	1454	26175	ACCACGAAAGCAAGAAAAA	3105
26175	UAUUCUUGCUAGUCACACU	1455	26175	UAUUCUUGCUAGUCACACU	1455	26193	AGUGUGACUAGCAAGAAUA	3106
26193	UAGCCAUCCUUACUGCGCU	1456	26193	UAGCCAUCCUUACUGCGCU	1456	26211	AGCGCAGUAAGGAUGGCUA	3107
26211	UUCGAUUGUGUGCGUACUG	1457	26211	UUCGAUUGUGUGCGUACUG	1457	26229	CAGUACGCACACAAUCGAA	3108
26229	GCUGCAAUAUUGUUAACGU	1458	26229	GCUGCAAUAUUGUUAACGU	1458	26247	ACGUUAACAAUAUUGCAGC	3109
26247	UGAGUUUAGUAAAACCAAC	1459	26247	UGAGUUUAGUAAAACCAAC	1459	26265	GUUGGUUUUACUAAACUCA	3110
26265	CGGUUUACGUCUACUCGCG	1460	26265	CGGUUUACGUCUACUCGCG	1460	26283	CGCGAGUAGACGUAAACCG	3111
26283	GUGUUAAAAAUCUGAACUC	1461	26283	GUGUUAAAAAUCUGAACUC	1461	26301	GAGUUCAGAUUUUUAACAC	3112
26301	CUUCUGAAGGAGUUCCUGA	1462	26301	CUUCUGAAGGAGUUCCUGA	1462	26319	UCAGGAACUCCUUCAGAAG	3113
26319	AUCUUCUGGUCUAAACGAA	1463	26319	AUCUUCUGGUCUAAACGAA	1463	26337	UUCGUUUAGACCAGAAGAU	3114
26337	ACUAACUAUUAUUAUUAUU	1464	26337	ACUAACUAUUAUUAUUAUU	1464	26355	AAUAAUAAUAAUAGUUAGU	3115

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26355	UCUGUUUGGAACUUUAACA	1465	26355	UCUGUUUGGAACUUUAACA	1465	26373	UGUUAAAGUUCCAAACAGA	3116
26373	AUUGCUUAUCAUGGCAGAC	1466	26373	AUUGCUUAUCAUGGCAGAC	1466	26391	GUCUGCCAUGAUAAGCAAU	3117
26391	CAACGGUACUAUUACCGUU	1467	26391	CAACGGUACUAUUACCGUU	1467	26409	AACGGUAAUAGUACCGUUG	3118
26409	UGAGGAGCUUAAACAACUC	1468	26409	UGAGGAGCUUAAACAACUC	1468	26427	GAGUUGUUUAAGCUCCUCA	3119
26427	CCUGGAACAAUGGAACCUA	1469	26427	CCUGGAACAAUGGAACCUA	1469	26445	UAGGUUCCAUUGUUCCAGG	3120
26445	AGUAAUAGGUUUCCUAUUC	1470	26445	AGUAAUAGGUUUCCUAUUC	1470	26463	GAAUAGGAAACCUAUUACU	3121
26463	CCUAGCCUGGAUUAUGUUA	1471	26463	CCUAGCCUGGAUUAUGUUA	1471	26481	UAACAUAAUCCAGGCUAGG	3122
26481	ACUACAAUUUGCCUAUUCU	1472	26481	ACUACAAUUUGCCUAUUCU	1472	26499	AGAAUAGGCAAAUUGUAGU	3123
26499	UAAUCGGAACAGGUUUUUG	1473	26499	UAAUCGGAACAGGUUUUUG	1473	26517	CAAAAACCUGUUCCGAUUA	3124
26517	GUACAUAAUAAAGCUUGUU	1474	26517	GUACAUAAUAAAGCUUGUU	1474	26535	AACAAGCUUUAUUAUGUAC	3125
26535	UUUCCUCUGGCUCUUGUGG	1475	26535	UUUCCUCUGGCUCUUGUGG	1475	26553	CCACAAGAGCCAGAGGAAA	3126
26553	GCCAGUAACACUUGCUUGU	1476	26553	GCCAGUAACACUUGCUUGU	1476	26571	ACAAGCAAGUGUUACUGGC	3127
26571	UUUUGUGCUUGCUGCUGUC	1477	26571	UUUUGUGCUUGCUGCUGUC	1477	26589	GACAGCAGCAAGCACAAAA	3128
26589	CUACAGAAUUAAUUGGGUG	1478	26589	CUACAGAAUUAAUUGGGUG	1478	26607	CACCCAAUUAAUUCUGUAG	3129
26607	GACUGGCGGGAUUGCGAUU	1479	26607	GACUGGCGGGAUUGCGAUU	1479	26625	AAUCGCAAUCCCGCCAGUC	3130
26625	UGCAAUGGCUUGUAUUGUA	1480	26625	UGCAAUGGCUUGUAUUGUA	1480	26643	UACAAUACAAGCCAUUGCA	3131
26643	AGGCUUGAUGUGGCUUAGC	1481	26643	AGGCUUGAUGUGGCUUAGC	1481	26661	GCUAAGCCACAUCAAGCCU	3132
26661	CUACUUCGUUGCUUCCUUC	1482	26661	CUACUUCGUUGCUUCCUUC	1482	26679	GAAGGAAGCAACGAAGUAG	3133
26679	CAGGCUGUUUGCUCGUACC	1483	26679	CAGGCUGUUUGCUCGUACC	1483	26697	GGUACGAGCAAACAGCCUG	3134
26697	CCGCUCAAUGUGGUCAUUC	1484	26697	CCGCUCAAUGUGGUCAUUC	1484	26715	GAAUGACCACAUUGAGCGG	3135
26715	CAACCCAGAAACAAACAUU	1485	26715	CAACCCAGAAACAAACAUU	1485	26733	AAUGUUUGUUUCUGGGUUG	3136
26733	UCUUCUCAAUGUGCCUCUC	1486	26733	UCUUCUCAAUGUGCCUCUC	1486	26751	GAGAGGCACAUUGAGAAGA	3137
26751	CCGGGGGACAAUUGUGACC	1487	26751	CCGGGGGACAAUUGUGACC	1487	26769	GGUCACAAUUGUCCCCCGG	3138
26769	CAGACCGCUCAUGGAAAGU	1488	26769	CAGACCGCUCAUGGAAAGU	1488	26787	ACUUUCCAUGAGCGGUCUG	3139
26787	UGAACUUGUCAUUGGUGCU	1489	26787	UGAACUUGUCAUUGGUGCU	1489	26805	AGCACCAAUGACAAGUUCA	3140
26805	UGUGAUCAUUCGUGGUCAC	1490	26805	UGUGAUCAUUCGUGGUCAC	1490	26823	GUGACCACGAAUGAUCACA	3141
26823	CUUGCGAAUGGCCGGACAC	1491	26823	CUUGCGAAUGGCCGGACAC	1491	26841	GUGUCCGGCCAUUCGCAAG	3142
26841	CUCCCUAGGGCGCUGUGAC	1492	26841	CUCCCUAGGGCGCUGUGAC	1492	26859	GUCACAGCGCCCUAGGGAG	3143
26859	CAUUAAGGACCUGCCAAAA	1493	26859	CAUUAAGGACCUGCCAAAA	1493	26877	UUUUGGCAGGUCCUUAAUG	3144
26877	AGAGAUCACUGUGGCUACA	1494	26877	AGAGAUCACUGUGGCUACA	1494	26895	UGUAGCCACAGUGAUCUCU	3145
26895	AUCACGAACGCUUUCUUAU	1495	26895	AUCACGAACGCUUUCUUAU	1495	26913	AUAAGAAAGCGUUCGUGAU	3146
26913	UUACAAAUUAGGAGCGUCG	1496	26913	UUACAAAUUAGGAGCGUCG	1496	26931	CGACGCUCCUAAUUUGUAA	3147
26931	GCAGCGUGUAGGCACUGAU	1497	26931	GCAGCGUGUAGGCACUGAU	1497	26949	AUCAGUGCCUACACGCUGC	3148
26949	UUCAGGUUUUGCUGCAUAC	1498	26949	UUCAGGUUUUGCUGCAUAC	1498	26967	GUAUGCAGCAAAACCUGAA	3149
26967	CAACCGCUACCGUAUUGGA	1499	26967	CAACCGCUACCGUAUUGGA	1499	26985	UCCAAUACGGUAGCGGUUG	3150
26985	AAACUAUAAAUUAAAUACA	1500	26985	AAACUAUAAAUUAAAUACA	1500	27003	UGUAUUUAAUUUAUAGUUU	3151
27003	AGACCACGCCGGUAGCAAC	1501	27003	AGACCACGCCGGUAGCAAC	1501	27021	GUUGCUACCGGCGUGGUCU	3152
27021	CGACAAUAUUGCUUUGCUA	1502	27021	CGACAAUAUUGCUUUGCUA	1502	27039	UAGCAAAGCAAUAUUGUCG	3153
27039	AGUACAGUAAGUGACAACA	1503	27039	AGUACAGUAAGUGACAACA	1503	27057	UGUUGUCACUUACUGUACU	3154
27057	AGAUGUUUCAUCUUGUUGA	1504	27057	AGAUGUUUCAUCUUGUUGA	1504	27075	UCAACAAGAUGAAACAUCU	3155
27075	ACUUCCAGGUUACAAUAGC	1505	27075	ACUUCCAGGUUACAAUAGC	1505	27093	GCUAUUGUAACCUGGAAGU	3156
27093	CAGAGAUAUUGAUUAUCAU	1506	27093	CAGAGAUAUUGAUUAUCAU	1506	27111	AUGAUAAUCAAUAUCUCUG	3157

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27111	UUAUGAGGACUUUCAGGAU	1507	27111	UUAUGAGGACUUUCAGGAU	1507	27129	AUCCUGAAAGUCCUCAUAA	3158
27129	UUGCUAUUUGGAAUCUUGA	1508	27129	UUGCUAUUUGGAAUCUUGA	1508	27147	UCAAGAUUCCAAAUAGCAA	3159
27147	ACGUUAUAAUAAGUUCAAU	1509	27147	ACGUUAUAAUAAGUUCAAU	1509	27165	AUUGAACUUAUUAUAACGU	3160
27165	UAGUGAGACAAUUAUUUAA	1510	27165	UAGUGAGACAAUUAUUUAA	1510	27183	UUAAAUAAUUGUCUCACUA	3161
27183	AGCCUCUAACUAAGAAGAA	1511	27183	AGCCUCUAACUAAGAAGAA	1511	27201	UUCUUCUUAGUUAGAGGCU	3162
27201	AUUAUUCGGAGUUAGAUGA	1512	27201	AUUAUUCGGAGUUAGAUGA	1512	27219	UCAUCUAACUCCGAAUAAU	3163
27219	AUGAAGAACCUAUGGAGUU	1513	27219	AUGAAGAACCUAUGGAGUU	1513	27237	AACUCCAUAGGUUCUUCAU	3164
27237	UAGAUUAUCCAUAAAACGA	1514	27237	UAGAUUAUCCAUAAAACGA	1514	27255	UCGUUUUAUGGAUAAUCUA	3165
27255	AACAUGAAAAUUAUUCUCU	1515	27255	AACAUGAAAAUUAUUCUCU	1515	27273	AGAGAAUAAUUUUCAUGUU	3166
27273	UUCCUGACAUUGAUUGUAU	1516	27273	UUCCUGACAUUGAUUGUAU	1516	27291	AUACAAUCAAUGUCAGGAA	3167
27291	UUUACAUCUUGCGAGCUAU	1517	27291	UUUACAUCUUGCGAGCUAU	1517	27309	AUAGCUCGCAAGAUGUAAA	3168
27309	UAUCACUAUCAGGAGUGUG	1518	27309	UAUCACUAUCAGGAGUGUG	1518	27327	CACACUCCUGAUAGUGAUA	3169
27327	GUUAGAGGUACGACUGUAC	1519	27327	GUUAGAGGUACGACUGUAC	1519	27345	GUACAGUCGUACCUCUAAC	3170
27345	CUACUAAAAGAACCUUGCC	1520	27345	CUACUAAAAGAACCUUGCC	1520	27363	GGCAAGGUUCUUUUAGUAG	3171
27363	CCAUCAGGAACAUACGAGG	1521	27363	CCAUCAGGAACAUACGAGG	1521	27381	CCUCGUAUGUUCCUGAUGG	3172
27381	GGCAAUUCACCAUUUCACC	1522	27381	GGCAAUUCACCAUUUCACC	1522	27399	GGUGAAAUGGUGAAUUGCC	3173
27399	CCUCUUGCUGACAAUAAAU	1523	27399	CCUCUUGCUGACAAUAAAU	1523	27417	AUUUAUUGUCAGCAAGAGG	3174
27417	UUUGCACUAACUUGCACUA	1524	27417	UUUGCACUAACUUGCACUA	1524	27435	UAGUGCAAGUUAGUGCAAA	3175
27435	AGCACACACUUUGCUUUUG	1525	27435	AGCACACACUUUGCUUUUG	1525	27453	CAAAAGCAAAGUGUGUGCU	3176
27453	GCUUGUGCUGACGGUACUC	1526	27453	GCUUGUGCUGACGGUACUC	1526	27471	GAGUACCGUCAGCACAAGC	3177
27471	CGACAUACCUAUCAGCUGC	1527	27471	CGACAUACCUAUCAGCUGC	1527	27489	GCAGCUGAUAGGUAUGUCG	3178
27489	CGUGCAAGAUCAGUUUCAC	1528	27489	CGUGCAAGAUCAGUUUCAC	1528	27507	GUGAAACUGAUCUUGCACG	3179
27507	CCAAAACUUUUCAUCAGAC	1529	27507	CCAAAACUUUUCAUCAGAC	1529	27525	GUCUGAUGAAAAGUUUUGG	3180
27525	CAAGAGGAGGUUCAACAAG	1530	27525	CAAGAGGAGGUUCAACAAG	1530	27543	CUUGUUGAACCUCCUCUUG	3181
27543	GAGCUCUACUCGCCACUUU	1531	27543	GAGCUCUACUCGCCACUUU	1531	27561	AAAGUGGCGAGUAGAGCUC	3182
27561	UUUCUCAUUGUUGCUGCUC	1532	27561	UUUCUCAUUGUUGCUGCUC	1532	27579	GAGCAGCAACAAUGAGAAA	3183
27579	CUAGUAUUUUUAAUACUUU	1533	27579	CUAGUAUUUUUAAUACUUU	1533	27597	AAAGUAUUAAAAAUACUAG	3184
27597	UGCUUCACCAUUAAGAGAA	1534	27597	UGCUUCACCAUUAAGAGAA	1534	27615	UUCUCUUAAUGGUGAAGCA	3185
27615	AAGACAGAAUGAAUGAGCU	1535	27615	AAGACAGAAUGAAUGAGCU	1535	27633	AGCUCAUUCAUUCUGUCUU	3186
27633	UCACUUUAAUUGACUUCUA	1536	27633	UCACUUUAAUUGACUUCUA	1536	27651	UAGAAGUCAAUUAAAGUGA	3187
27651	AUUUGUGCUUUUUAGCCUU	1537	27651	AUUUGUGCUUUUUAGCCUU	1537	27669	AAGGCUAAAAAGCACAAAU	3188
27669	UUCUGCUAUUCCUUGUUUU	1538	27669	UUCUGCUAUUCCUUGUUUU	1538	27687	AAAACAAGGAAUAGCAGAA	3189
27687	UAAUAAUGCUUAUUAUAUU	1539	27687	UAAUAAUGCUUAUUAUAUU	1539	27705	AAUAUAAUAAGCAUUAUUA	3190
27705	UUUGGUUUUCACUCGAAAU	1540	27705	UUUGGUUUUCACUCGAAAU	1540	27723	AUUUCGAGUGAAAACCAAA	3191
27723	UCCAGGAUCUAGAAGAACC	1541	27723	UCCAGGAUCUAGAAGAACC	1541	27741	GGUUCUUCUAGAUCCUGGA	3192
27741	CUUGUACCAAAGUCUAAAC	1542	27741	CUUGUACCAAAGUCUAAAC	1542	27759	GUUUAGACUUUGGUACAAG	3193
27759	CGAACAUGAAACUUCUCAU	1543	27759	CGAACAUGAAACUUCUCAU	1543	27777	AUGAGAAGUUUCAUGUUCG	3194
27777	UUGUUUUGACUUGUAUUUC	1544	27777	UUGUUUUGACUUGUAUUUC	1544	27795	GAAAUACAAGUCAAAACAA	3195
27795	CUCUAUGCAGUUGCAUAUG	1545	27795	CUCUAUGCAGUUGCAUAUG	1545	27813	CAUAUGCAACUGCAUAGAG	3196
27813	GCACUGUAGUACAGCGCUG	1546	27813	GCACUGUAGUACAGCGCUG	1546	27831	CAGCGCUGUACUACAGUGC	3197
27831	GUGCAUCUAAUAAACCUCA	1547	27831	GUGCAUCUAAUAAACCUCA	1547	27849	UGAGGUUUAUUAGAUGCAC	3198
27849	AUGUGCUUGAAGAUCCUUG	1548	27849	AUGUGCUUGAAGAUCCUUG	1548	27867	CAAGGAUCUUCAAGCACAU	3199

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27867	GUAAGGUACAACACUAGGG	1549	27867	GUAAGGUACAACACUAGGG	1549	27885	CCCUAGUGUUGUACCUUAC	3200
27885	GGUAAUACUUAUAGCACUG	1550	27885	GGUAAUACUUAUAGCACUG	1550	27903	CAGUGCUAUAAGUAUUACC	3201
27903	GCUUGGCUUUGUGCUCUAG	1551	27903	GCUUGGCUUUGUGCUCUAG	1551	27921	CUAGAGCACAAAGCCAAGC	3202
27921	GGAAAGGUUUUACCUUUUC	1552	27921	GGAAAGGUUUUACCUUUUC	1552	27939	GAAAAGGUAAAACCUUUCC	3203
27939	CAUAGAUGGCACACUAUGG	1553	27939	CAUAGAUGGCACACUAUGG	1553	27957	CCAUAGUGUGCCAUCUAUG	3204
27957	GUUCAAACAUGCACACCUA	1554	27957	GUUCAAACAUGCACACCUA	1554	27975	UAGGUGUGCAUGUUUGAAC	3205
27975	AAUGUUACUAUCAACUGUC	1555	27975	AAUGUUACUAUCAACUGUC	1555	27993	GACAGUUGAUAGUAACAUU	3206
27993	CAAGAUCCAGCUGGUGGUG	1556	27993	CAAGAUCCAGCUGGUGGUG	1556	28011	CACCACCAGCUGGAUCUUG	3207
28011	GCGCUUAUAGCUAGGUGUU	1557	28011	GCGCUUAUAGCUAGGUGUU	1557	28029	AACACCUAGCUAUAAGCGC	3208
28029	UGGUACCUUCAUGAAGGUC	1558	28029	UGGUACCUUCAUGAAGGUC	1558	28047	GACCUUCAUGAAGGUACCA	3209
28047	CACCAAACUGCUGCAUUUA	1559	28047	CACCAAACUGCUGCAUUUA	1559	28065	UAAAUGCAGCAGUUUGGUG	3210
28065	AGAGACGUACUUGUUGUUU	1560	28065	AGAGACGUACUUGUUGUUU	1560	28083	AAACAACAAGUACGUCUCU	3211
28083	UUAAAUAAACGAACAAAUU	1561	28083	UUAAAUAAACGAACAAAUU	1561	28101	AAUUUGUUCGUUUAUUUAA	3212
28101	UAAAAUGUCUGAUAAUGGA	1562	28101	UAAAAUGUCUGAUAAUGGA	1562	28119	UCCAUUAUCAGACAUUUUA	3213
28119	ACCCCAAUCAAACCAACGU	1563	28119	ACCCCAAUCAAACCAACGU	1563	28137	ACGUUGGUUUGAUUGGGGU	3214
28137	UAGUGCCCCCGCAUUACA	1564	28137	UAGUGCCCCCGCAUUACA	1564	28155	UGUAAUGCGGGGGCACUA	3215
28155	AUUUGGUGGACCCACAGAU	1565	28155	AUUUGGUGGACCCACAGAU	1565	28173	AUCUGUGGGUCCACCAAAU	3216
28173	UUCAACUGACAAUAACCAG	1566	28173	UUCAACUGACAAUAACCAG	1566	28191	CUGGUUAUUGUCAGUUGAA	3217
28191	GAAUGGAGGACGCAAUGGG	1567	28191	GAAUGGAGGACGCAAUGGG	1567	28209	CCCAUUGCGUCCUCCAUUC	3218
28209	GGCAAGGCCAAAACAGCGC	1568	28209	GGCAAGGCCAAAACAGCGC	1568	28227	GCGCUGUUUUGGCCUUGCC	3219
28227	CCGACCCCAAGGUUUACCC	1569	28227	CCGACCCCAAGGUUUACCC	1569	28245	GGGUAAACCUUGGGGUCGG	3220
28245	CAAUAAUACUGCGUCUUGG	1570	28245	CAAUAAUACUGCGUCUUGG	1570	28263	CCAAGACGCAGUAUUAUUG	3221
28263	GUUCACAGCUCUCACUCAG	1571	28263	GUUCACAGCUCUCACUCAG	1571	28281	CUGAGUGAGAGCUGUGAAC	3222
28281	GCAUGGCAAGGAGGAACUU	1572	28281	GCAUGGCAAGGAGGAACUU	1572	28299	AAGUUCCUCCUUGCCAUGC	3223
28299	UAGAUUCCCUCGAGGCCAG	1573	28299	UAGAUUCCCUCGAGGCCAG	1573	28317	CUGGCCUCGAGGGAAUCUA	3224
28317	GGGCGUUCCAAUCAACACC	1574	28317	GGGCGUUCCAAUCAACACC	1574	28335	GGUGUUGAUUGGAACGCCC	3225
28335	CAAUAGUGGUCCAGAUGAC	1575	28335	CAAUAGUGGUCCAGAUGAC	1575	28353	GUCAUCUGGACCACUAUUG	3226
28353	CCAAAUUGGCUACUACCGA	1576	28353	CCAAAUUGGCUACUACCGA	1576	28371	UCGGUAGUAGCCAAUUUGG	3227
28371	AAGAGCUACCCGACGAGUU	1577	28371	AAGAGCUACCCGACGAGUU	1577	28389	AACUCGUCGGGUAGCUCUU	3228
28389	UCGUGGUGGUGACGGCAAA	1578	28389	UCGUGGUGGUGACGGCAAA	1578	28407	UUUGCCGUCACCACCACGA	3229
28407	AAUGAAAGAGCUCAGCCCC	1579	28407	AAUGAAAGAGCUCAGCCCC	1579	28425	GGGGCUGAGCUCUUUCAUU	3230
28425	CAGAUGGUACUUCUAUUAC	1580	28425	CAGAUGGUACUUCUAUUAC	1580	28443	GUAAUAGAAGUACCAUCUG	3231
28443	CCUAGGAACUGGCCCAGAA	1581	28443	CCUAGGAACUGGCCCAGAA	1581	28461	UUCUGGGCCAGUUCCUAGG	3232
28461	AGCUUCACUUCCCUACGGC	1582	28461	AGCUUCACUUCCCUACGGC	1582	28479	GCCGUAGGGAAGUGAAGCU	3233
28479	CGCUAACAAAGAAGGCAUC	1583	28479	CGCUAACAAAGAAGGCAUC	1583	28497	GAUGCCUUCUUUGUUAGCG	3234
28497	CGUAUGGGUUGCAACUGAG	1584	28497	CGUAUGGGUUGCAACUGAG	1584	28515	CUCAGUUGCAACCCAUACG	3235
28515	GGGAGCCUUGAAUACACCC	1585	28515	GGGAGCCUUGAAUACACCC	1585	28533	GGGUGUAUUCAAGGCUCCC	3236
28533	CAAAGACCACAUUGGCACC	1586	28533	CAAAGACCACAUUGGCACC	1586	28551	GGUGCCAAUGUGGUCUUUG	3237
28551	CCGCAAUCCUAAUAACAAU	1587	28551	CCGCAAUCCUAAUAACAAU	1587	28569	AUUGUUAUUAGGAUUGCGG	3238
28569	UGCUGCCACCGUGCUACAA	1588	28569	UGCUGCCACCGUGCUACAA	1588	28587	UUGUAGCACGGUGGCAGCA	3239
28587	ACUUCCUCAAGGAACAACA	1589	28587	ACUUCCUCAAGGAACAACA	1589	28605	UGUUGUUCCUUGAGGAAGU	3240
28605	AUUGCCAAAAGGCUUCUAC	1590	28605	AUUGCCAAAAGGCUUCUAC	1590	28623	GUAGAAGCCUUUUGGCAAU	3241

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28623	CGCAGAGGGAAGCAGAGGC	1591	28623	CGCAGAGGGAAGCAGAGGC	1591	28641	GCCUCUGCUUCCCUCUGCG	3242
28641	CGGCAGUCAAGCCUCUUCU	1592	28641	CGGCAGUCAAGCCUCUUCU	1592	28659	AGAAGAGGCUUGACUGCCG	3243
28659	UCGCUCCUCAUCACGUAGU	1593	28659	UCGCUCCUCAUCACGUAGU	1593	28677	ACUACGUGAUGAGGAGCGA	3244
28677	UCGCGGUAAUUCAAGAAAU	1594	28677	UCGCGGUAAUUCAAGAAAU	1594	28695	AUUUCUUGAAUUACCGCGA	3245
28695	UUCAACUCCUGGCAGCAGU	1595	28695	UUCAACUCCUGGCAGCAGU	1595	28713	ACUGCUGCCAGGAGUUGAA	3246
28713	UAGGGGAAAUUCUCCUGCU	1596	28713	UAGGGGAAAUUCUCCUGCU	1596	28731	AGCAGGAGAAUUUCCCCUA	3247
28731	UCGAAUGGCUAGCGGAGGU	1597	28731	UCGAAUGGCUAGCGGAGGU	1597	28749	ACCUCCGCUAGCCAUUCGA	3248
28749	UGGUGAAACUGCCCUCGCG	1598	28749	UGGUGAAACUGCCCUCGCG	1598	28767	CGCGAGGGCAGUUUCACCA	3249
28767	GCUAUUGCUGCUAGACAGA	1599	28767	GCUAUUGCUGCUAGACAGA	1599	28785	UCUGUCUAGCAGCAAUAGC	3250
28785	AUUGAACCAGCUUGAGAGC	1600	28785	AUUGAACCAGCUUGAGAGC	1600	28803	GCUCUCAAGCUGGUUCAAU	3251
28803	CAAAGUUUCUGGUAAAGGC	1601	28803	CAAAGUUUCUGGUAAAGGC	1601	28821	GCCUUUACCAGAAACUUUG	3252
28821	CCAACAACAACAAGGCCAA	1602	28821	CCAACAACAACAAGGCCAA	1602	28839	UUGGCCUUGUUGUUGUUGG	3253
28839	AACUGUCACUAAGAAAUCU	1603	28839	AACUGUCACUAAGAAAUCU	1603	28857	AGAUUUCUUAGUGACAGUU	3254
28857	UGCUGCUGAGGCAUCUAAA	1604	28857	UGCUGCUGAGGCAUCUAAA	1604	28875	UUUAGAUGCCUCAGCAGCA	3255
28875	AAAGCCUCGCCAAAAACGU	1605	28875	AAAGCCUCGCCAAAAACGU	1605	28893	ACGUUUUUGGCGAGGCUUU	3256
28893	UACUGCCACAAAACAGUAC	1606	28893	UACUGCCACAAAACAGUAC	1606	28911	GUACUGUUUUGUGGCAGUA	3257
28911	CAACGUCACUCAAGCAUUU	1607	28911	CAACGUCACUCAAGCAUUU	1607	28929	AAAUGCUUGAGUGACGUUG	3258
28929	UGGGAGACGUGGUCCAGAA	1608	28929	UGGGAGACGUGGUCCAGAA	1608	28947	UUCUGGACCACGUCUCCCA	3259
28947	ACAAACCCAAGGAAAUUUC	1609	28947	ACAAACCCAAGGAAAUUUC	1609	28965	GAAAUUUCCUUGGGUUUGU	3260
28965	CGGGGACCAAGACCUAAUC	1610	28965	CGGGGACCAAGACCUAAUC	1610	28983	GAUUAGGUCUUGGUCCCCG	3261
28983	CAGACAAGGAACUGAUUAC	1611	28983	CAGACAAGGAACUGAUUAC	1611	29001	GUAAUCAGUUCCUUGUCUG	3262
29001	CAAACAUUGGCCGCAAAUU	1612	29001	CAAACAUUGGCCGCAAAUU	1612	29019	AAUUUGCGGCCAAUGUUUG	3263
29019	UGCACAAUUUGCUCCAAGU	1613	29019	UGCACAAUUUGCUCCAAGU	1613	29037	ACUUGGAGCAAAUUGUGCA	3264
29037	UGCCUCUGCAUUCUUUGGA	1614	29037	UGCCUCUGCAUUCUUUGGA	1614	29055	UCCAAAGAAUGCAGAGGCA	3265
29055	AAUGUCACGCAUUGGCAUG	1615	29055	AAUGUCACGCAUUGGCAUG	1615	29073	CAUGCCAAUGCGUGACAUU	3266
29073	GGAAGUCACACCUUCGGGA	1616	29073	GGAAGUCACACCUUCGGGA	1616	29091	UCCCGAAGGUGUGACUUCC	3267
29091	AACAUGGCUGACUUAUCAU	1617	29091	AACAUGGCUGACUUAUCAU	1617	29109	AUGAUAAGUCAGCCAUGUU	3268
29109	UGGAGCCAUUAAAUUGGAU	1618	29109	UGGAGCCAUUAAAUUGGAU	1618	29127	AUCCAAUUUAAUGGCUCCA	3269
29127	UGACAAAGAUCCACAAUUC	1619	29127	UGACAAAGAUCCACAAUUC	1619	29145	GAAUUGUGGAUCUUUGUCA	3270
29145	CAAAGACAACGUCAUACUG	1620	29145	CAAAGACAACGUCAUACUG	1620	29163	CAGUAUGACGUUGUCUUUG	3271
29163	GCUGAACAAGCACAUUGAC	1621	29163	GCUGAACAAGCACAUUGAC	1621	29181	GUCAAUGUGCUUGUUCAGC	3272
29181	CGCAUACAAAACAUUCCCA	1622	29181	CGCAUACAAAACAUUCCCA	1622	29199	UGGGAAUGUUUUGUAUGCG	3273
29199	ACCAACAGAGCCUAAAAAG	1623	29199	ACCAACAGAGCCUAAAAAG	1623	29217	CUUUUUAGGCUCUGUUGGU	3274
29217	GGACAAAAAGAAAAAGACU	1624	29217	GGACAAAAAGAAAAAGACU	1624	29235	AGUCUUUUUCUUUUUGUCC	3275
29235	UGAUGAAGCUCAGCCUUUG	1625	29235	UGAUGAAGCUCAGCCUUUG	1625	29253	CAAAGGCUGAGCUUCAUCA	3276
29253	GCCGCAGAGACAAAAGAAG	1626	29253	GCCGCAGAGACAAAAGAAG	1626	29271	CUUCUUUUGUCUCUGCGGC	3277
29271	GCAGCCCACUGUGACUCUU	1627	29271	GCAGCCCACUGUGACUCUU	1627	29289	AAGAGUCACAGUGGGCUGC	3278
29289	UCUUCCUGCGGCUGACAUG	1628	29289	UCUUCCUGCGGCUGACAUG	1628	29307	CAUGUCAGCCGCAGGAAGA	3279
29307	GGAUGAUUUCUCCAGACAA	1629	29307	GGAUGAUUUCUCCAGACAA	1629	29325	UUGUCUGGAGAAAUCAUCC	3280
29325	ACUUCAAAAUUCCAUGAGU	1630	29325	ACUUCAAAAUUCCAUGAGU	1630	29343	ACUCAUGGAAUUUUGAAGU	3281
29343	UGGAGCUUCUGCUGAUUCA	1631	29343	UGGAGCUUCUGCUGAUUCA	1631	29361	UGAAUCAGCAGAAGCUCCA	3282
29361	AACUCAGGCAUAAACACUC	1632	29361	AACUCAGGCAUAAACACUC	1632	29379	GAGUGUUUAUGCCUGAGUU	3283

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29379	CAUGAUGACCACACAAGGC	1633	29379	CAUGAUGACCACACAAGGC	1633	29397	GCCUUGUGUGGUCAUCAUG	3284
29397	CAGAUGGGCUAUGUAAACG	1634	29397	CAGAUGGGCUAUGUAAACG	1634	29415	CGUUUACAUAGCCCAUCUG	3285
29415	GUUUUCGCAAUUCCGUUUA	1635	29415	GUUUUCGCAAUUCCGUUUA	1635	29433	UAAACGGAAUUGCGAAAAC	3286
29433	ACGAUACAUAGUCUACUCU	1636	29433	ACGAUACAUAGUCUACUCU	1636	29451	AGAGUAGACUAUGUAUCGU	3287
29451	UUGUGCAGAAUGAAUUCUC	1637	29451	UUGUGCAGAAUGAAUUCUC	1637	29469	GAGAAUUCAUUCUGCACAA	3288
29469	CGUAACUAAACAGCACAAG	1638	29469	CGUAACUAAACAGCACAAG	1638	29487	CUUGUGCUGUUUAGUUACG	3289
29487	GUAGGUUUAGUUAACUUUA	1639	29487	GUAGGUUUAGUUAACUUUA	1639	29505	UAAAGUUAACUAAACCUAC	3290
29505	AAUCUCACAUAGCAAUCUU	1640	29505	AAUCUCACAUAGCAAUCUU	1640	29523	AAGAUUGCUAUGUGAGAUU	3291
29523	UUAAUCAAUGUGUAACAUU	1641	29523	UUAAUCAAUGUGUAACAUU	1641	29541	AAUGUUACACAUUGAUUAA	3292
29541	UAGGGAGGACUUGAAAGAG	1642	29541	UAGGGAGGACUUGAAAGAG	1642	29559	CUCUUUCAAGUCCUCCCUA	3293
29559	GCCACCACAUUUUCAUCGA	1643	29559	GCCACCACAUUUUCAUCGA	1643	29577	UCGAUGAAAAUGUGGUGGC	3294
29577	AGGCCACGCGGAGUACGAU	1644	29577	AGGCCACGCGGAGUACGAU	1644	29595	AUCGUACUCCGCGUGGCCU	3295
29595	UCGAGGGUACAGUGAAUAA	1645	29595	UCGAGGGUACAGUGAAUAA	1645	29613	UUAUUCACUGUACCCUCGA	3296
29613	AUGCUAGGGAGAGCUGCCU	1646	29613	AUGCUAGGGAGAGCUGCCU	1646	29631	AGGCAGCUCUCCCUAGCAU	3297
29631	UAUAUGGAAGAGCCCUAAU	1647	29631	UAUAUGGAAGAGCCCUAAU	1647	29649	AUUAGGGCUCUUCCAUAUA	3298
29649	UGUGUAAAAUUAAUUUUAG	1648	29649	UGUGUAAAAUUAAUUUUAG	1648	29667	CUAAAAUUAAUUUUACACA	3299
29667	GUAGUGCUAUCCCCAUGUG	1649	29667	GUAGUGCUAUCCCCAUGUG	1649	29685	CACAUGGGGAUAGCACUAC	3300
29685	GAUUUUAAUAGCUUCUUAG	1650	29685	GAUUUUAAUAGCUUCUUAG	1650	29703	CUAAGAAGCUAUUAAAAUC	3301
29703	GGAGAAUGACAAAAAAAAA	1651	29703	GGAGAAUGACAAAAAAAAA	1651	29721	UUUUUUUUUGUCAUUCUCC	3302

The 3'-ends of the Upper sequence and the Lower sequence of the siNA construct can include an overhang sequence, for example about 1, 2, 3, or 4 nucleotides in length, preferably 2 nucleotides in length, wherein the overhanging sequence of the lower sequence is optionally complementary to a portion of the target sequence. The overhang can comprise the general structure B, BNN, NN, BNsN, or NsN, where B stands for any terminal cap moiety, N stands for any nucleotide (e.g., thymidine) and s stands for phosphorothioate or other internucleotide linkage as described herein (e.g. internucleotide linkage having Formula I). The upper sequence is also referred to as the sense strand, whereas the lower sequence is also referred to as the antisense strand. The upper and lower sequences in the Table can further comprise a chemical modification having Formulae I-VII or any combination thereof (see for example chemical modifications as shown in Table V herein).

Table III: SARS synthetic siNA and Target Sequences

Target Pos	Target	SeqID	RPI#	Aliases	Sequence	SeqID
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1657U21 siRNA sense	AAUGAAGAGGUUGCCAUCATT	3311
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA sense	UUGCAUCUCCACAGGAGUGTT	3312
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2383U21 siRNA sense	CAAAGCAAGGGACUUUACCTT	3313
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA sense	GUGUAAAUGGCCUCAUGCUTT	3314
26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA sense	UGUGCUUGCUGCUGUCUACTT	3315
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26792U21 siRNA sense	UUGUCAUUGGUGCUGUGAUTT	3316
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA sense	GAACCAGCUUGAGAGCAAATT	3317
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA sense	UUGUUUUCCUCUGGCUCUUTT	3318
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) antisense	UGAUGGCAACCUCUUCAUUTT	3319
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) antisense	CACUCCUGUGGAGAUGCAATT	3320
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2401L21 siRNA (2383C) antisense	GGUAAAGUCCCUUGCUUUGTT	3321
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) antisense	AGCAUGAGGCCAUUUACACTT	3322
26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) antisense	GUAGACAGCAGCAAGCACATT	3323
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26810L21 siRNA (26792C) antisense	AUCACAGCACCAAUGACAATT	3324
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) antisense	UUUGCUCUCAAGCUGGUUCTT	3325
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26549L21 siRNA (26531C) antisense	AAGAGCCAGAGGAAAACAATT	3326
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1657U21 siRNA stab04 sense	B AAuGAAGAGGuuGccAucATT B	3327
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA stab04 sense	B uuGcAucuccAcAGGAGuGTT B	3328
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2383U21 siRNA stab04 sense	B cAAAGcAAGGGAcuuuAccTT B	3329
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA stab04 sense	B GuGuAAAuGGccucAuGcuTT B	3330
26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA stab04 sense	B uGuGcuuGcuGcuGucuAcTT B	3331
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26792U21 siRNA stab04 sense	B uuGucAuuGGuGcuGuGAuTT B	3332
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA stab04 sense	B GAAccAGcuuGAGAGcAAATT B	3333
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA stab04 sense	B uuGuuuuccucuGGcucuuTT B	3334
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) stab05 antisense	uGAuGGcAAccucuucAuuTsT	3335
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab05 antisense	cAcuccuGuGGAGAuGcAATsT	3336

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2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2401L21 siRNA (2383C) stab05 antisense	GGuAAAGucccuuGcuuuGTsT	3337
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) stab05 antisense	AGcAuGAGGccAuuuAcAcTsT	3338
26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) stab05 antisense	GuAGAcAGcAGcAAGcAcATsT	3339
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26810L21 siRNA (26792C) stab05 antisense	AucAcAGcAccAAuGAcAATsT	3340
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) stab05 antisense	uuuGcucucAAGcuGGuucTsT	3341
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26549L21 siRNA (26531C) stab05 antisense	AAGAGccAGAGGAAAAcAATsT	3342
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1657U21 siRNA stab07 sense	B AAuGAAGAGGuuGccAucATT B	3343
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA stab07 sense	B uuGcAucuccAcAGGAGuGTT B	3344
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2383U21 siRNA stab07 sense	B cAAAGcAAGGGAcuuuAccTT B	3345
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA stab07 sense	B GuGuAAAuGGccucAuGcuTT B	3346
26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA stab07 sense	B uGuGcuuGcuGcuGucuAcTT B	3347
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26792U21 siRNA stab07 sense	B uuGucAuuGGuGcuGuGAuTT B	3348
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA stab07 sense	B GAAccAGcuuGAGAGcAAATT B	3349
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA stab07 sense	B uuGuuuuccucuGGcucuuTT B	3350
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) stab11 antisense	uGAuGGcAAccucuucAuuTsT	3351
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab11 antisense	cAcuccuGuGGAGAuGcAATsT	3352
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2401L21 siRNA (2383C) stab11 antisense	GGuAAAGucccuuGcuuuGTsT	3353
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) stab11 antisense	AGcAuGAGGccAuuuAcAcTsT	3354
26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) stab11 antisense	GuAGAcAGcAGcAAGcAcATsT	3355
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26810L21 siRNA (26792C) stab11 antisense	AucAcAGcAccAAuGAcAATsT	3356
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) stab11 antisense	uuuGcucucAAGcuGGuucTsT	3357
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26549L21 siRNA (26531C) stab11 antisense	AAGAGccAGAGGAAAAcAATsT	3358
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1657U21 siRNA stab08 sense	AAuGAAGAGGuuGccAucATsT	3359
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA stab08 sense	uuGcAucuccAcAGGAGuGTsT	3360
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2383U21 siRNA stab08 sense	cAAAGcAAGGGAcuuuAccTsT	3361
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA stab08 sense	GuGuAAAuGGccucAuGcuTsT	3362

(400/110_US)

26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA stab08 sense	uGuGcuuGcuGcuGucuAcTsT	3363
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26792U21 siRNA stab08 sense	uuGucAuuGGuGcuGuGAuTsT	3364
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA stab08 sense	GAAccAGcuuGAGAGcAAATsT	3365
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA stab08 sense	uuGuuuuccucuGGcucuuTsT	3366
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) stab08 antisense	uGAuGGcAAccucuucAuuTsT	3367
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab08 antisense	cAcuccuGuGGAGAuGcAATsT	3368
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2401L21 siRNA (2383C) stab08 antisense	GGuAAAGucccuuGcuuuGTsT	3369
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) stab08 antisense	AGcAuGAGGccAuuuAcAcTsT	3370
26572	UUUGUGCUUGCUGCUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) stab08 antisense	GuAGAcAGcAGcAAGcAcATsT	3371
26790	ACUUGUCAUUGGUGCUGUGAUCA	3308		SARS:26810L21 siRNA (26792C) stab08 antisense	AucAcAGcAccAAuGAcAATsT	3372
28786	UUGAACCAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) stab08 antisense	uuuGcucucAAGcuGGuucTsT	3373
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26549L21 siRNA (26531C) stab08 antisense	AAGAGccAGAGGAAAAcAATsT	3374

Uppercase = ribonucleotide
u,c = 2'-deoxy-2'-fluoro U, C
A = 2'-O-methyl Adenosine
G = 2'-O-methyl Guanosine
T = thymidine
B = inverted deoxy abasic
s = phosphorothioate linkage
A = deoxy Adenosine
G = deoxy Guanosine

Table IV

Non-limiting examples of Stabilization Chemistries for chemically modified siNA constructs

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 00"	Ribo	Ribo	TT at 3'-ends		S/AS
"Stab 1"	Ribo	Ribo	-	5 at 5'-end 1 at 3'-end	S/AS
"Stab 2"	Ribo	Ribo	-	All linkages	Usually AS
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	Usually AS
"Stab 9"	Ribo	Ribo	5' and 3'-ends	-	Usually S
"Stab 10"	Ribo	Ribo	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 16	Ribo	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends	1 at 3'-end	Usually S
"Stab 19"	2'-fluoro	2'-O-Methyl	3'-end		Usually AS
"Stab 20"	2'-fluoro	2'-deoxy	3'-end		Usually AS
"Stab 21"	2'-fluoro	Ribo	3'-end		Usually AS
"Stab 22"	Ribo	Ribo	3'-end -		Usually AS

CAP = any terminal cap, see for example **Figure 10**.
All Stab 1-22 chemistries can comprise 3'-terminal thymidine (TT) residues
All Stab 1-22 chemistries typically comprise about 21 nucleotides, but can vary as described herein.
S = sense strand AS = antisense strand

Table V

A. 2.5 μmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	6.5	163 μL	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 μL	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 μL	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 μL	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 μL	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 μmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	15	31 μL	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 μL	45 sec	233 min	465 sec
Acetic Anhydride	655	124 μL	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 μL	5 sec	5 sec	5 sec
TCA	700	732 μL	10 sec	10 sec	10 sec
Iodine	20.6	244 μL	15 sec	15 sec	15 sec
Beaucage	7.7	232 μL	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 μmol Synthesis Cycle 96 well Instrument

Reagent	Equivalents:DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O-methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 μL	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 μL	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 μL	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 μL	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 μL	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 μL	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 μL	NA	NA	NA

- Wait time does not include contact time during delivery.
- Tandem synthesis utilizes double coupling of linker molecule

CLAIMS

What we claim is:

1. A chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a severe acute respiratory syndrome (SARS) virus RNA via RNA interference, wherein:

    a. each strand of said siNA molecule is about 19 to about 23 nucleotides in length;

    b. one strand of said siNA molecule comprises nucleotide sequence having sufficient complementarity to said SARS virus RNA for the siNA molecule to direct cleavage of the SARS virus RNA via RNA interference; and

    c. said siNA molecule does not require the presence of nucleotides having a 2'-hydroxy group for mediating RNA interference.

2. The siNA molecule of claim 1, wherein said siNA molecule comprises no ribonucleotides.

3. The siNA molecule of claim 1, wherein said siNA molecule comprises ribonucleotides.

4. The siNA molecule of claim 1, wherein one strand of said double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein a second strand of said double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of said SARS virus RNA.

5. The siNA molecule of claim 4, wherein each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and wherein each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand.

6. The siNA molecule of claim 1, wherein said siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein said siNA further comprises a sense region, wherein said sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of said SARS virus gene or a portion thereof.

7. The siNA molecule of claim 6, wherein said antisense region and said sense region comprises about 19 to about 23 nucleotides, and wherein said antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region.

8. The siNA molecule of claim 1, wherein said siNA molecule comprises a sense region and an antisense region, and wherein said antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS virus gene, or a portion thereof, and said sense region comprises a nucleotide sequence that is complementary to said antisense region.

9. The siNA molecule of claim 6, wherein said siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region of said siNA molecule.

10. The siNA molecule of claim claim 6, wherein said sense region is connected to the antisense region via a linker molecule.

11. The siNA molecule of claim 10, wherein said linker molecule is a polynucleotide linker.

12. The siNA molecule of claim 10, wherein said linker molecule is a non-nucleotide linker.

13. The siNA molecule of claim 6, wherein pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides.

14. The siNA molecule of claim 6, wherein purine nucleotides in the sense region are 2'-deoxy purine nucleotides.

15. The siNA molecule of claim 6, wherein pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

16. The siNA molecule of claim 9, wherein the fragment comprising said sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment comprising said sense region.

17. The siNA molecule of claim 16, wherein said terminal cap moiety is an inverted deoxy abasic moiety.

18. The siNA molecule of claim 6, wherein pyrimidine nucleotides of said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides

19. The siNA molecule of claim 6, wherein purine nucleotides of said antisense region are 2'-O-methyl purine nucleotides.

20. 20. The siNA molecule of claim 6, wherein purine nucleotides present in said antisense region comprise 2'-deoxy- purine nucleotides.

21. The siNA molecule of claim 18, wherein said antisense region comprises a phosphorothioate internucleotide linkage at the 3' end of said antisense region.

22. The siNA molecule of claim 6, wherein said antisense region comprises a glyceryl modification at the 3' end of said antisense region.

23. The siNA molecule of claim 9, wherein each of the two fragments of said siNA molecule comprise 21 nucleotides.

24. The siNA molecule of claim 23, wherein about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule.

25. The siNA molecule of claim 24, wherein each of the two 3' terminal nucleotides of each fragment of the siNA molecule are 2'-deoxy-pyrimidines.

26. The siNA molecule of claim 25, wherein said 2'-deoxy-pyrimidine is 2'-deoxy-thymidine.

27. The siNA molecule of claim 23, wherein all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule.

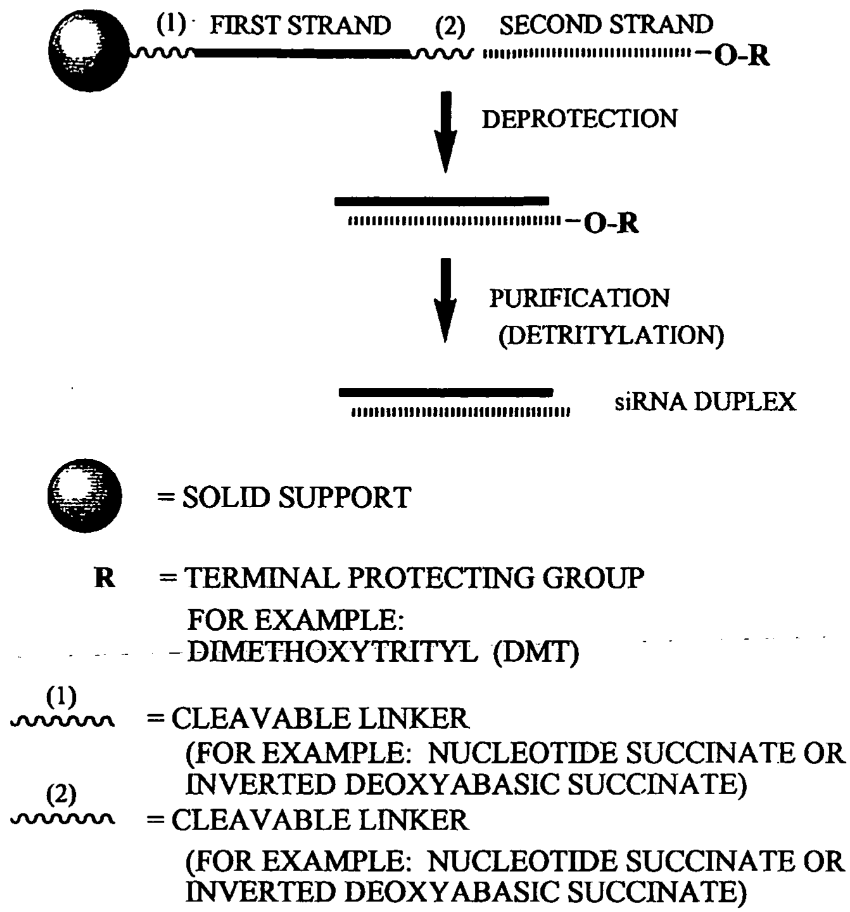
28. The siNA molecule of claim 23, wherein about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.

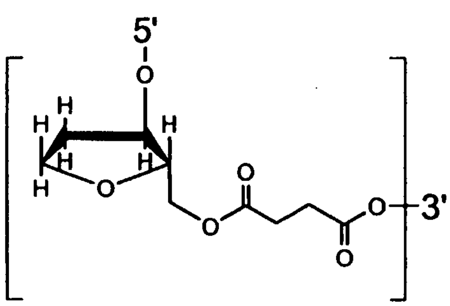
29. The siNA molecule of claim 23, wherein 21 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.

30. The siNA molecule of claim 9, wherein the 5'-end of the fragment comprising said antisense region optionally includes a phosphate group.

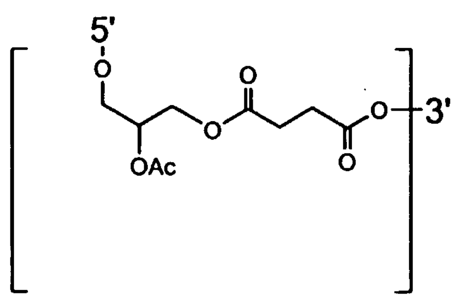
31. A pharmaceutical composition comprising the siNA molecule of claim 1 in an acceptable carrier or diluent.

Figure 1





INVERTED DEOXYABASIC SUCCINATE LINKAGE



GLYCERYL SUCCINATE LINKAGE

Figure 2

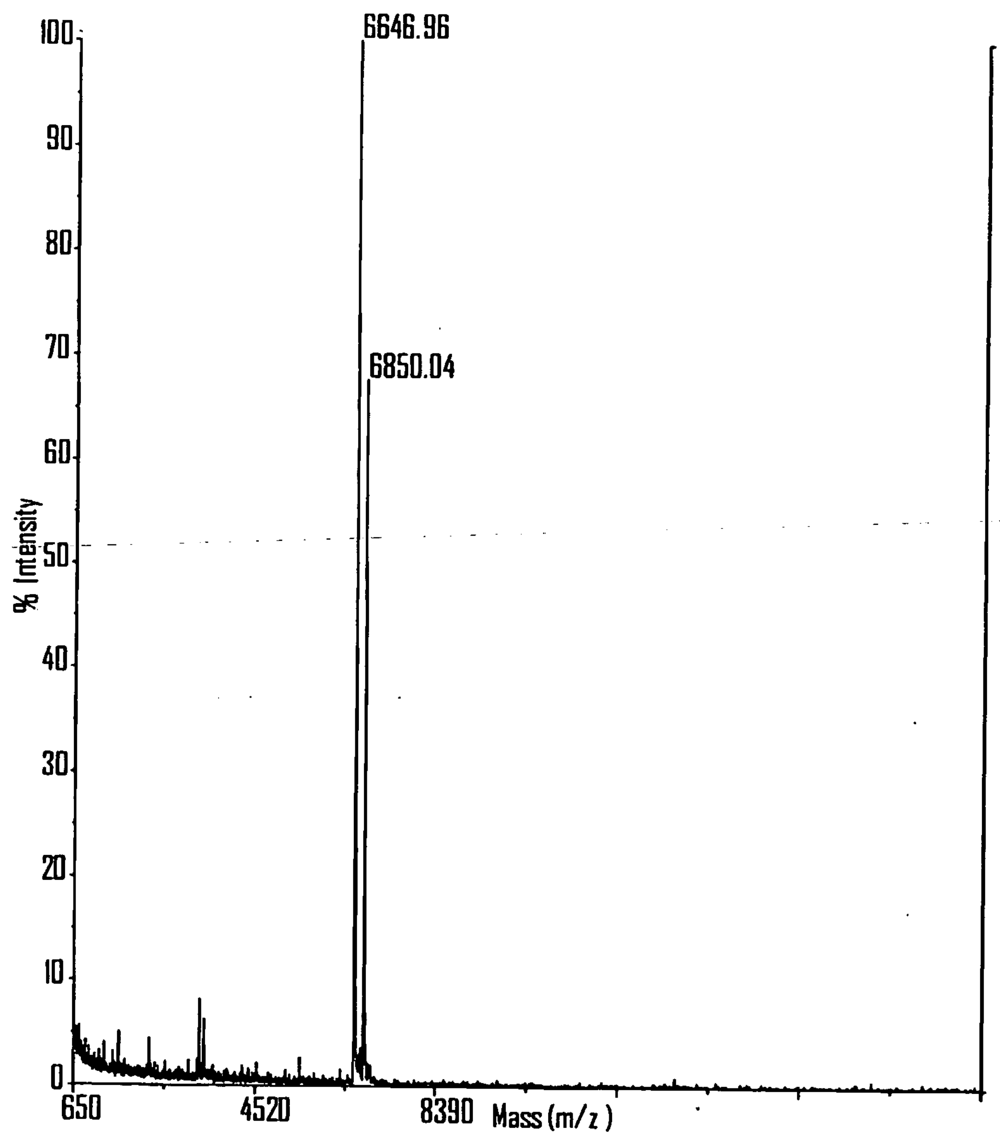

6646.96
6850.04
100
90
80
70
60
50
40
30
20
10
0
% Intensity
650
4520
8390
Mass (m/z)

Figure 3

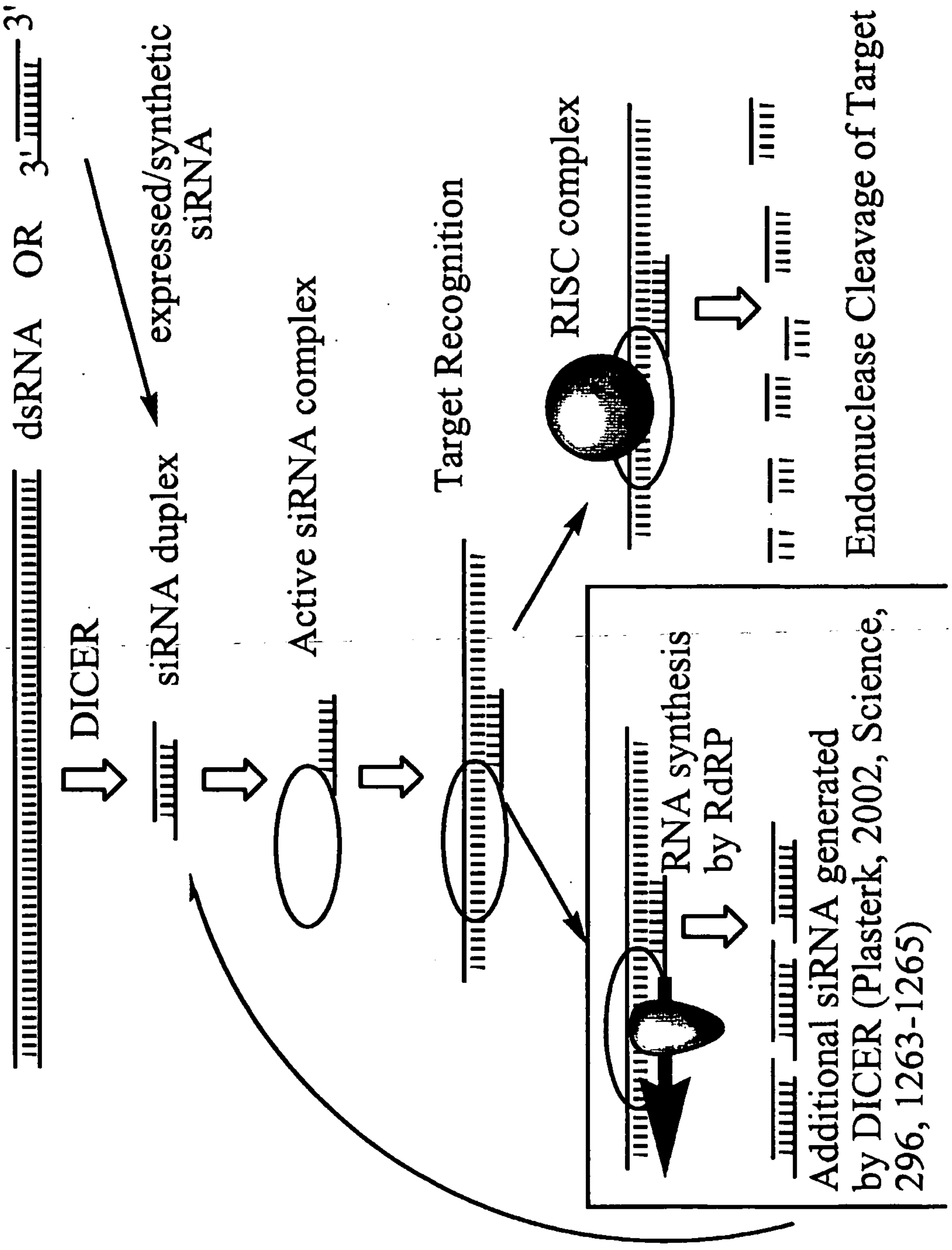

dsRNA OR 3' 3'
DICER
siRNA duplex
expressed/synthetic siRNA
Active siRNA complex
Target Recognition
RISC complex
Endonuclease Cleavage of Target
RNA synthesis by RdRP
Additional siRNA generated by DICER (Plasterk, 2002, Science, 296, 1263-1265)

Figure 4

A

SENSE STRAND (SEQ ID NO 3375)
ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 3376)
ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)

B

SENSE STRAND (SEQ ID NO 3377)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N)

5'- N N N N N N N N N N N N N N N N N N N (N_sN) -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 3378)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)

C

SENSE STRAND (SEQ ID NO 3379)
ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N)

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 3380)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)

D

SENSE STRAND (SEQ ID NO 3381)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 3378)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)

E

SENSE STRAND (SEQ ID NO 3382)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N N) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 3378)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)

F

SENSE STRAND (SEQ ID NO 3381)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 3383)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENTL = GLYCERYL or B THAT IS OPTIONALLY PRESENTS = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

Figure 5

A

SENSE STRAND (SEQ ID NO 3384)

5'- iB-A U G U G C U U G A A G A U C C U U G *T T*-iB -3'

3'- L-T_S*T*U A C A C G A A C U U C U A G G A A C -5'

ANTISENSE STRAND (SEQ ID NO 3385)

B

SENSE STRAND (SEQ ID NO 3386)

5'- a *u* g *u* g *c u u* g a a g a *u c c u u* g *T T* -3'

3'- L-T_S*T u* a *c* a *c* g a a *c u u c u* a g g a a *c* -5'

ANTISENSE STRAND (SEQ ID NO 3387)

C

SENSE STRAND (SEQ ID NO 3388)

5'- iB-A u G u G c u u G A A G A u c c u u G *T T*-iB -3'

3'- L-T_S*T u* A *c* A *c* G A A *c u u c u* A G G A A *c* -5'

ANTISENSE STRAND (SEQ ID NO 3389)

D

SENSE STRAND (SEQ ID NO 3390)

5'- iB-*A u G u G c u u G A A G A u c c u u G T T*-iB -3'

3'- L-T_S*T u* a *c* a *c* g a a *c u u c u* a g g a a *c* -5'

ANTISENSE STRAND (SEQ ID NO 3387)

E

SENSE STRAND (SEQ ID NO 3391)

5'- iB-A *u* G *u* G *c u u* G A A G A *u c c u u* G *T T*-iB -3'

3'- L-T_S*T u* a *c* a *c* g a a *c u u c u* a g g a a *c* -5'

ANTISENSE STRAND (SEQ ID NO 3387)

F

SENSE STRAND (SEQ ID NO 3390)

5'- iB-*A u G u G c u u G A A G A u c c u u G T T*-iB -3'

3'- L-T_S*T u A c A c G A A c u u c u A G G A A c* -5'

ANTISENSE STRAND (SEQ ID NO 3392)

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro
italic lower case = 2'-deoxy-2'-fluoro
underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY
iB = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY or iB OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE OPTIONALLY PRESEN

Figure 6

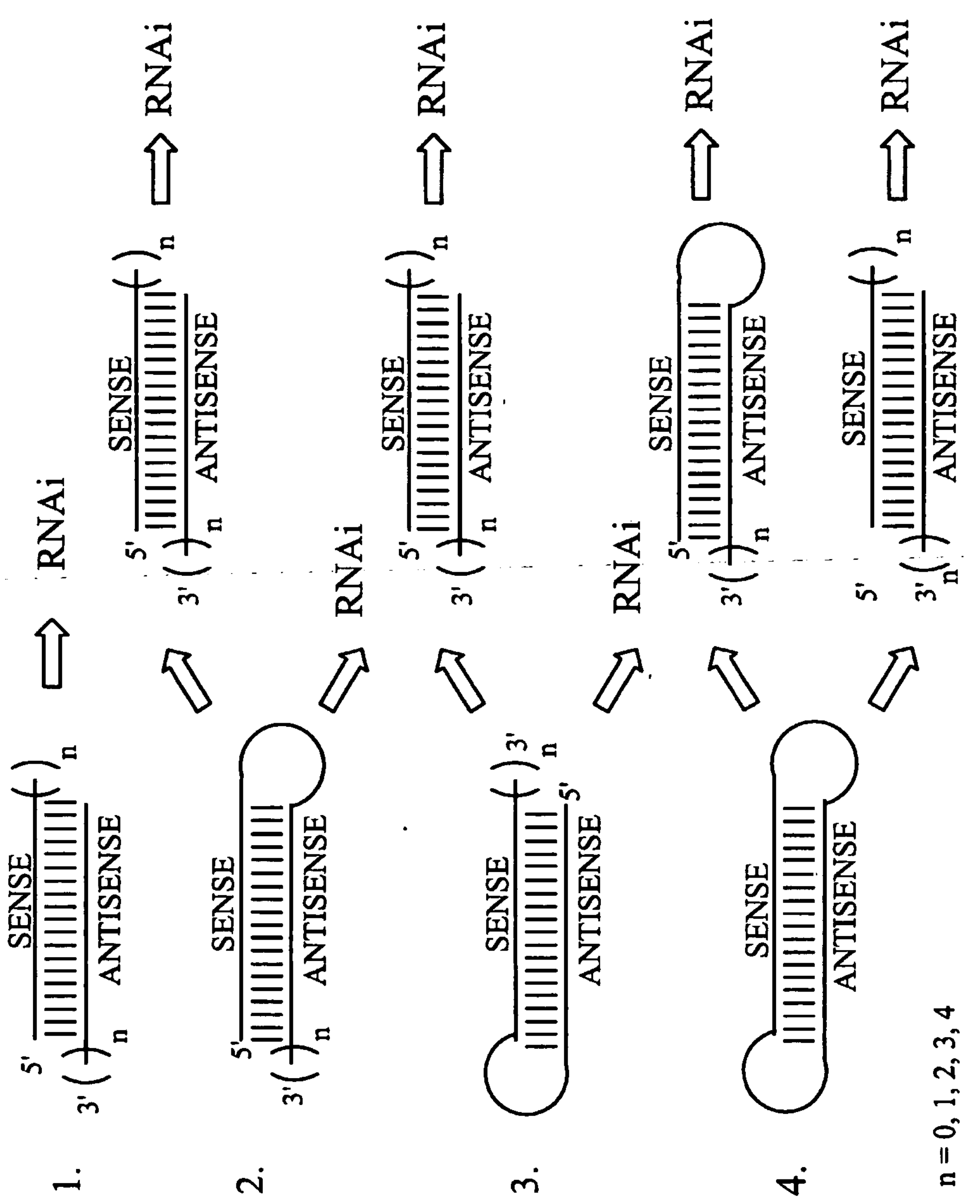


Figure 7

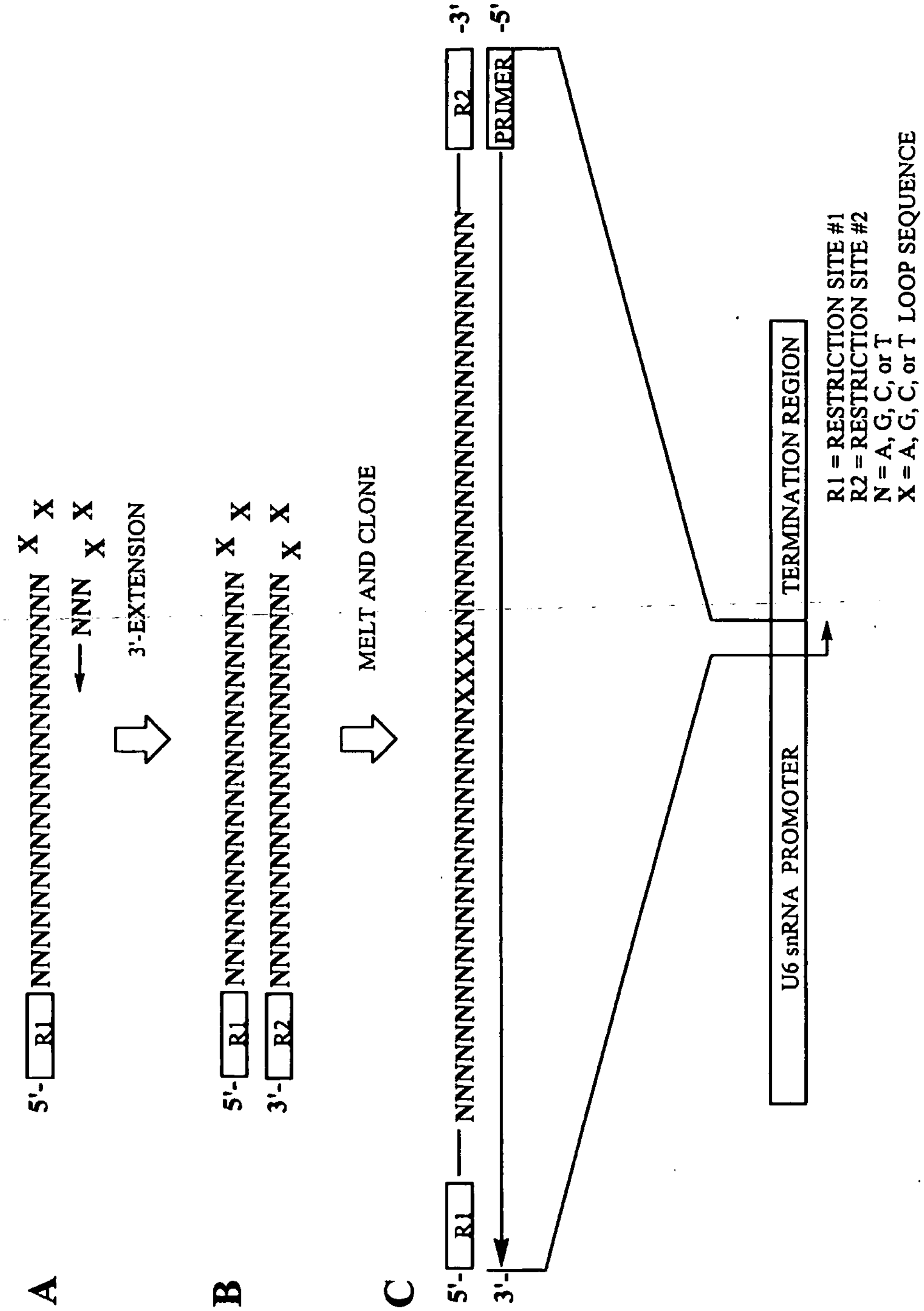

A
5'- R1 NNNNNNNNNNNNNNNNNNNNN X X
NNN X X
3'-EXTENSION
B
5'- R1 NNNNNNNNNNNNNNNNNNNNN X X
3'- R2 NNNNNNNNNNNNNNNNNNNNN X X
MELT AND CLONE
C
5'- R1 NNNNNNNNNNNNNNNNNNNNNXXXXNNNNNNNNNNNNNNNNNNNNN R2 -3'
3'- PRIMER -5'
U6 snRNA PROMOTER
TERMINATION REGION
R1 = RESTRICTION SITE #1
R2 = RESTRICTION SITE #2
N = A, G, C, or T
X = A, G, C, or T LOOP SEQUENCE

Figure 8

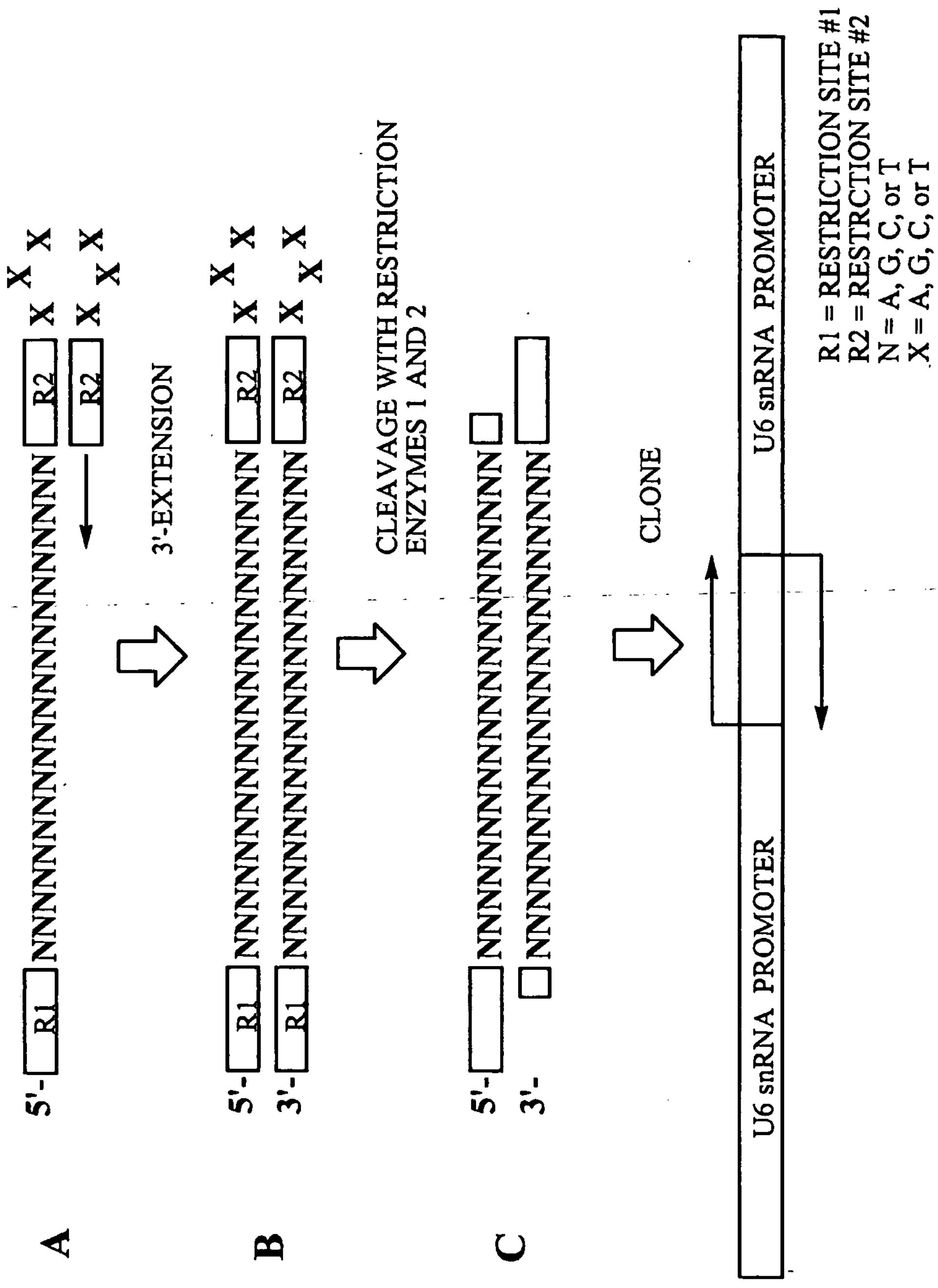

A
5'- R1 NNNNNNNNNNNNNNNNNNNNNNN R2 X X X X X X X
3'-EXTENSION
B
5'- R1 NNNNNNNNNNNNNNNNNNNNNNN R2 X X X X
3'- R1 NNNNNNNNNNNNNNNNNNNNNNN R2 X X X
CLEAVAGE WITH RESTRICTION ENZYMES 1 AND 2
C
5'- NNNNNNNNNNNNNNNNNNNNNNN
3'- NNNNNNNNNNNNNNNNNNNNNNN
CLONE
U6 snRNA PROMOTER
U6 snRNA PROMOTER
R1 = RESTRICTION SITE #1
R2 = RESTRCTION SITE #2
N = A, G, C, or T
X = A, G, C, or T

Figure 9: Target site Selection using siRNA

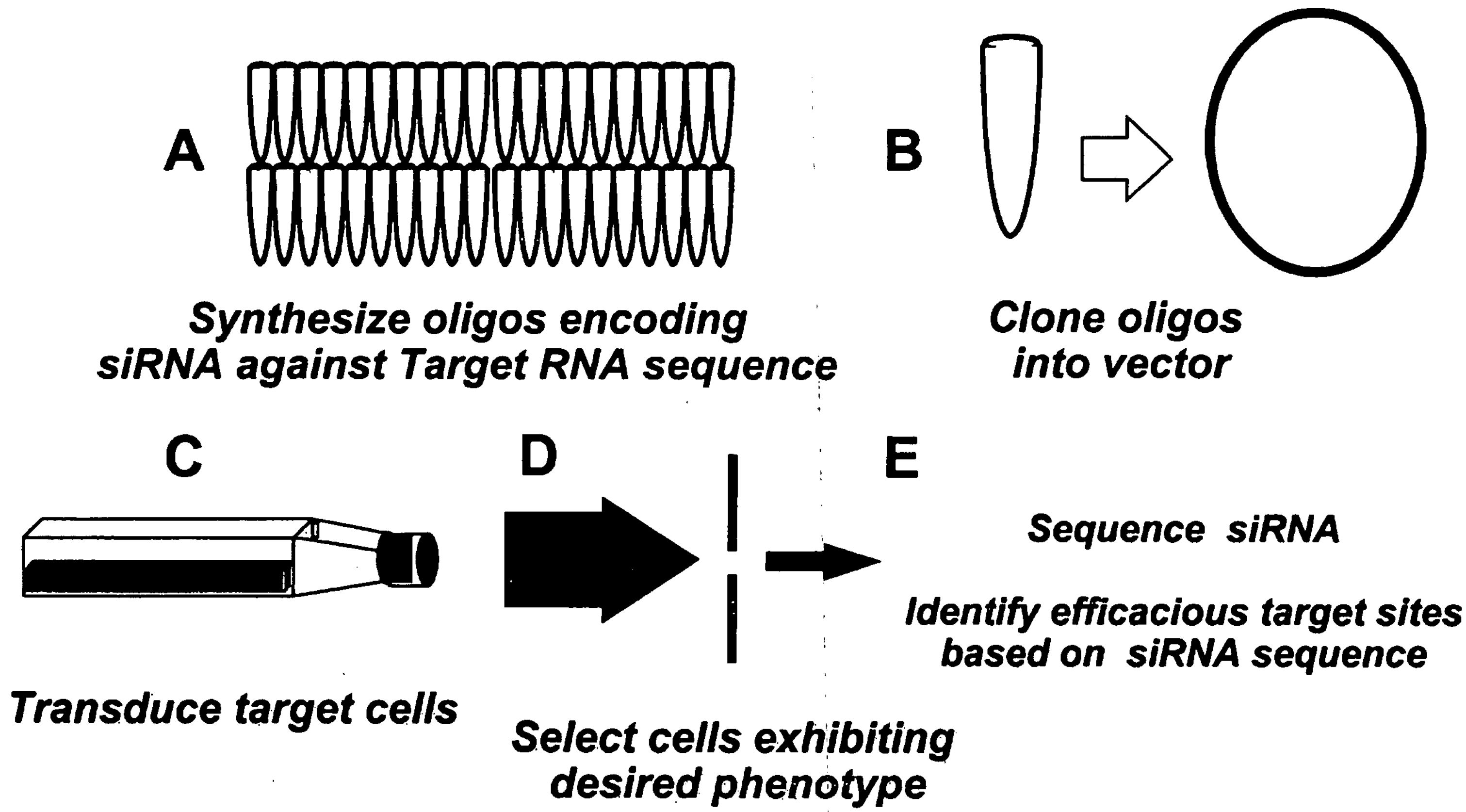
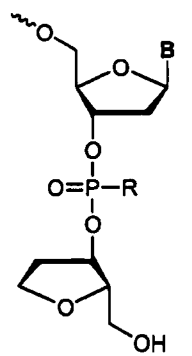


Figure 10



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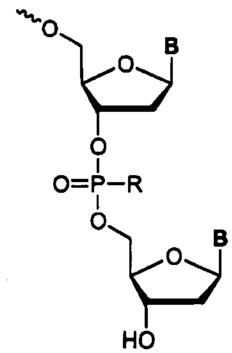

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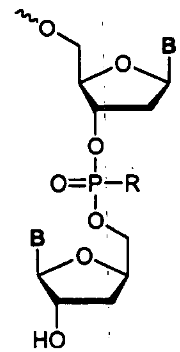

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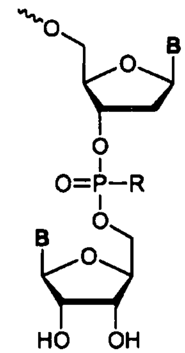

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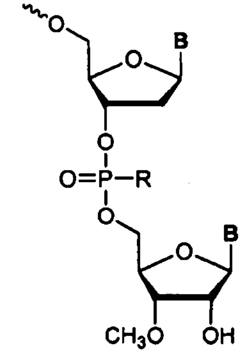

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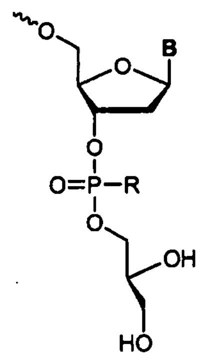
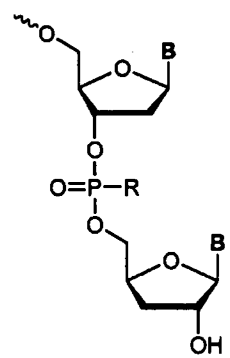
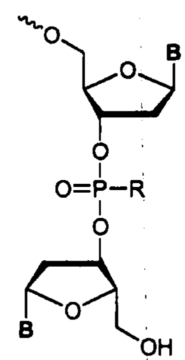


6



7



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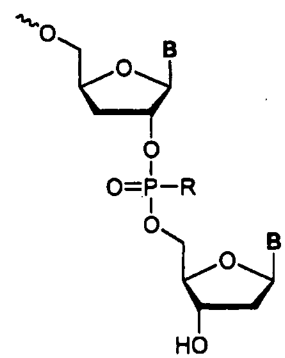

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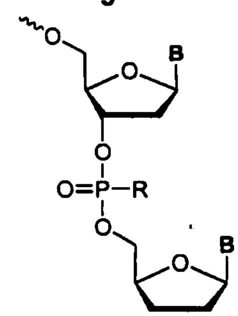


10

R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 11: Modification Strategy

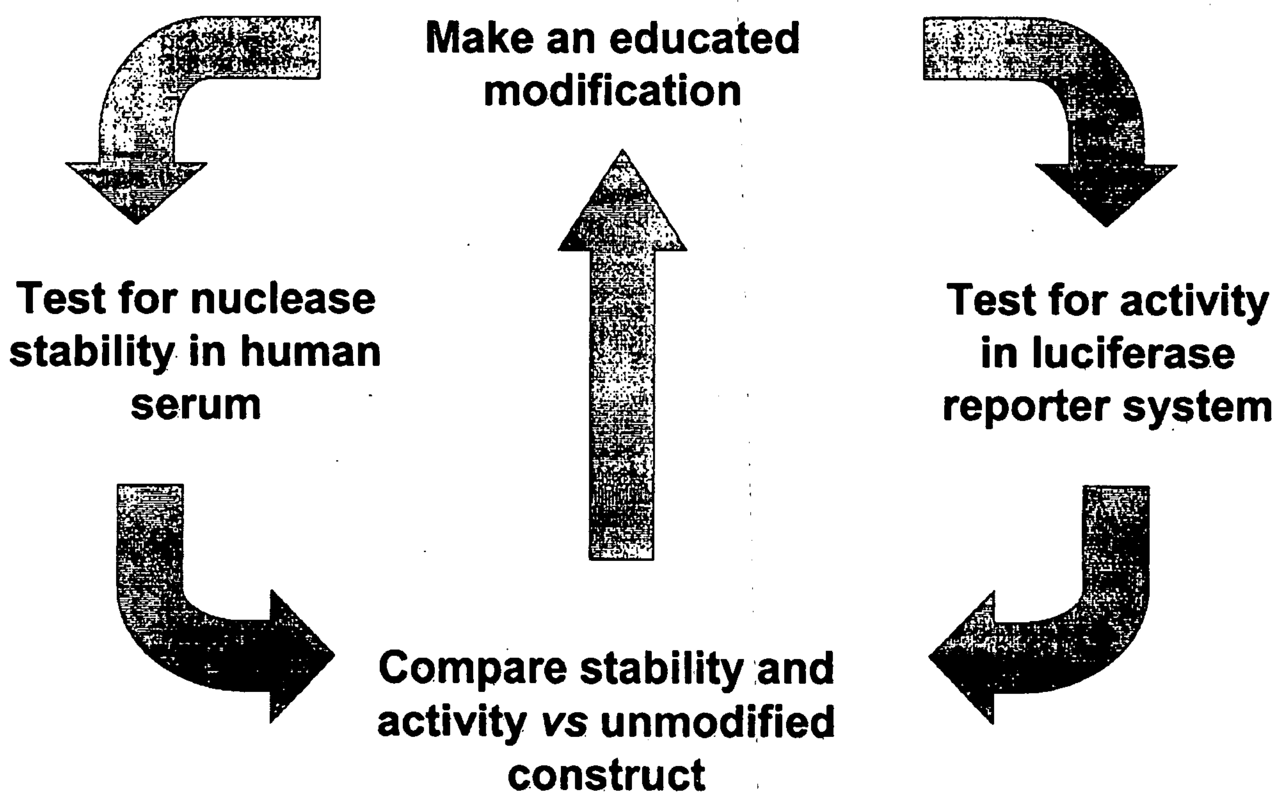


Figure 12: Phosphorylated siNA constructs

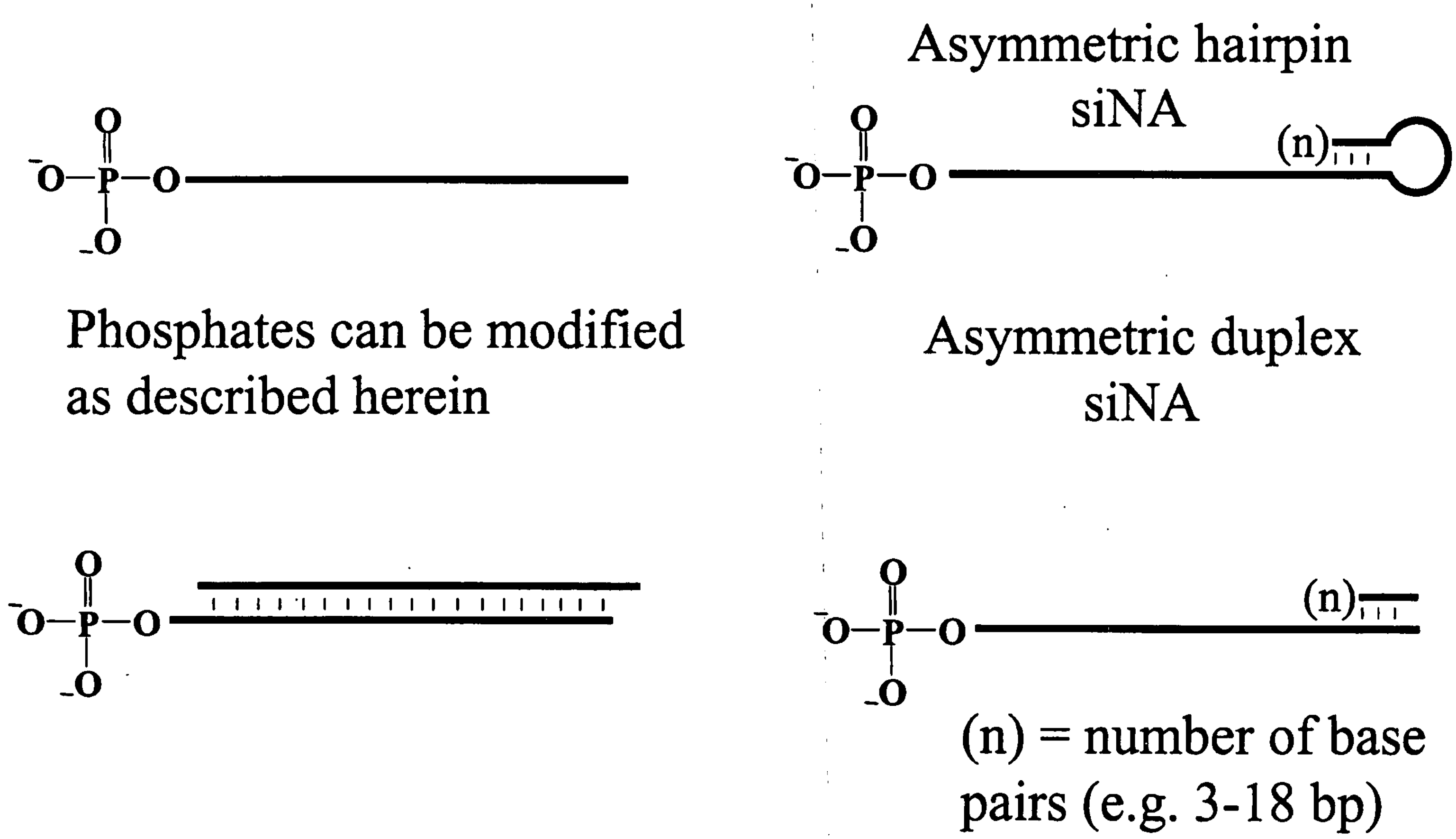


Figure 13: 5'-phosphate modifications

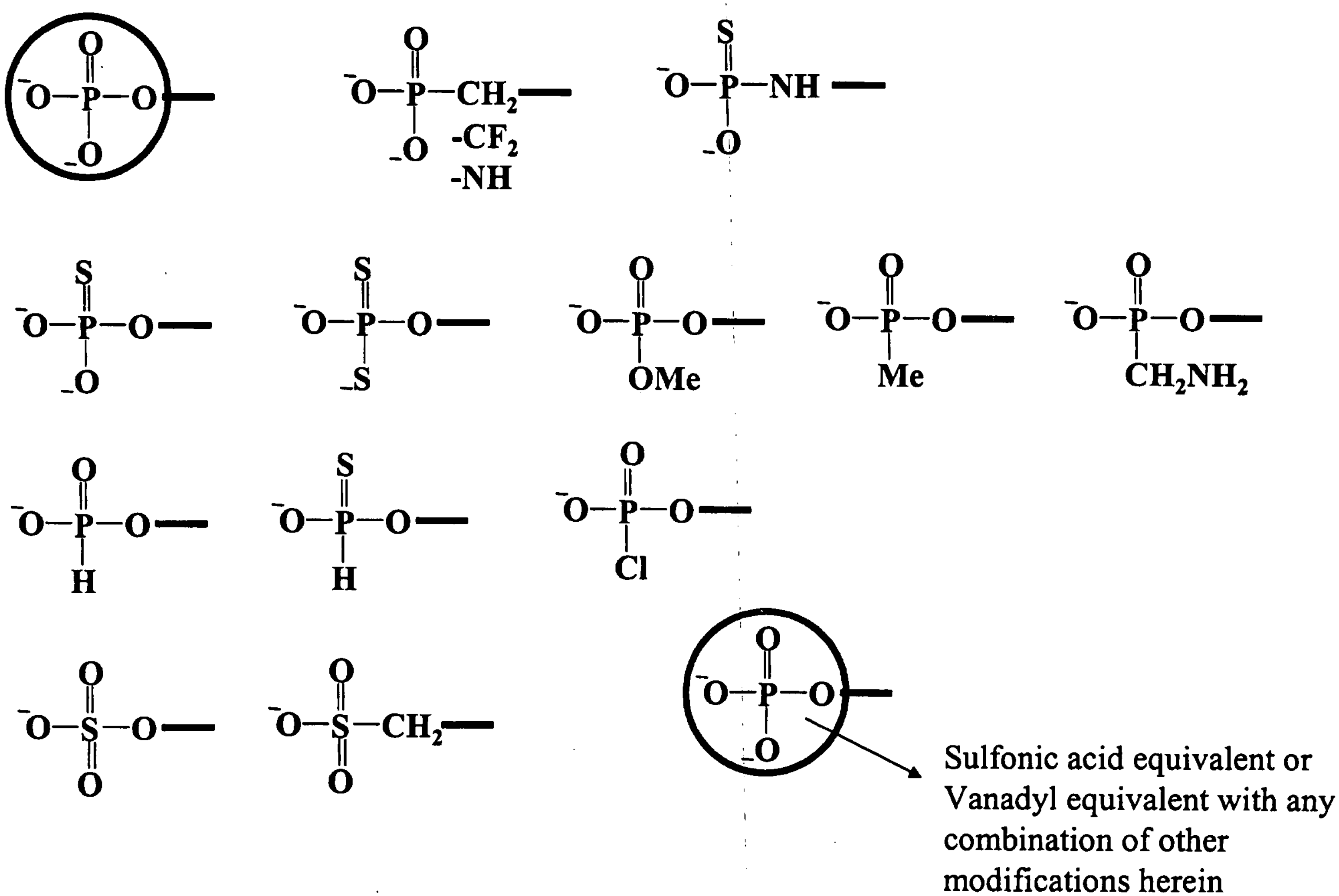
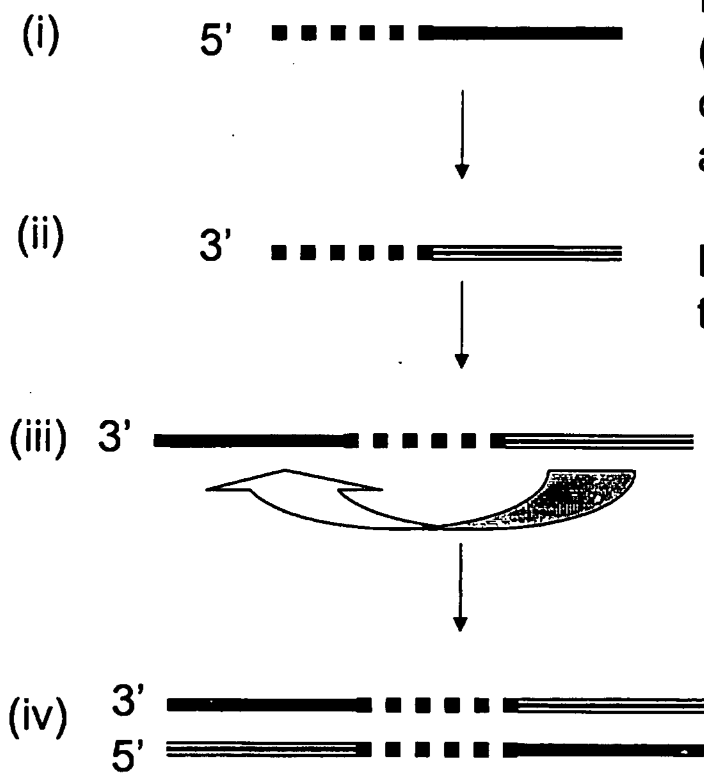


Figure 14A: Duplex forming oligonucleotide constructs that utilize palindrome or repeat sequences



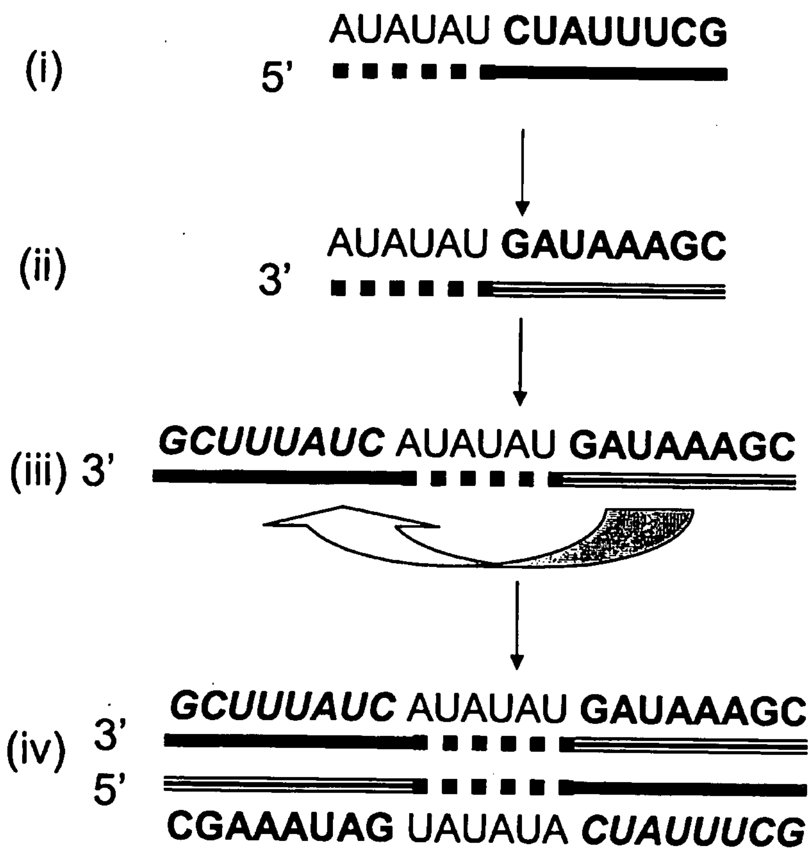
(i) Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length) containing palindrome/repeat sequence at 5'-end (dashed portion)

(ii) Design Complementary Sequence to the Target Nucleic Acid sequence of (i) above

(iii) Append inverse sequence of the Non-palindromic Complementary Sequence of (ii) to 3'-end of complementary sequence

(iv) Self assembly of self complementary strands to form duplex construct

Figure 14B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence



Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length) containing palindrome/repeat sequence at 5'-end (dashed portion)

Design Complementary Sequence to the Target Nucleic Acid sequence of (i) above

Append inverse sequence of the Non-palindromic Complementary Sequence of (ii) to 3'-end of complementary sequence

Self assembly of self complementary strands to form duplex construct (blunt ends)

Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

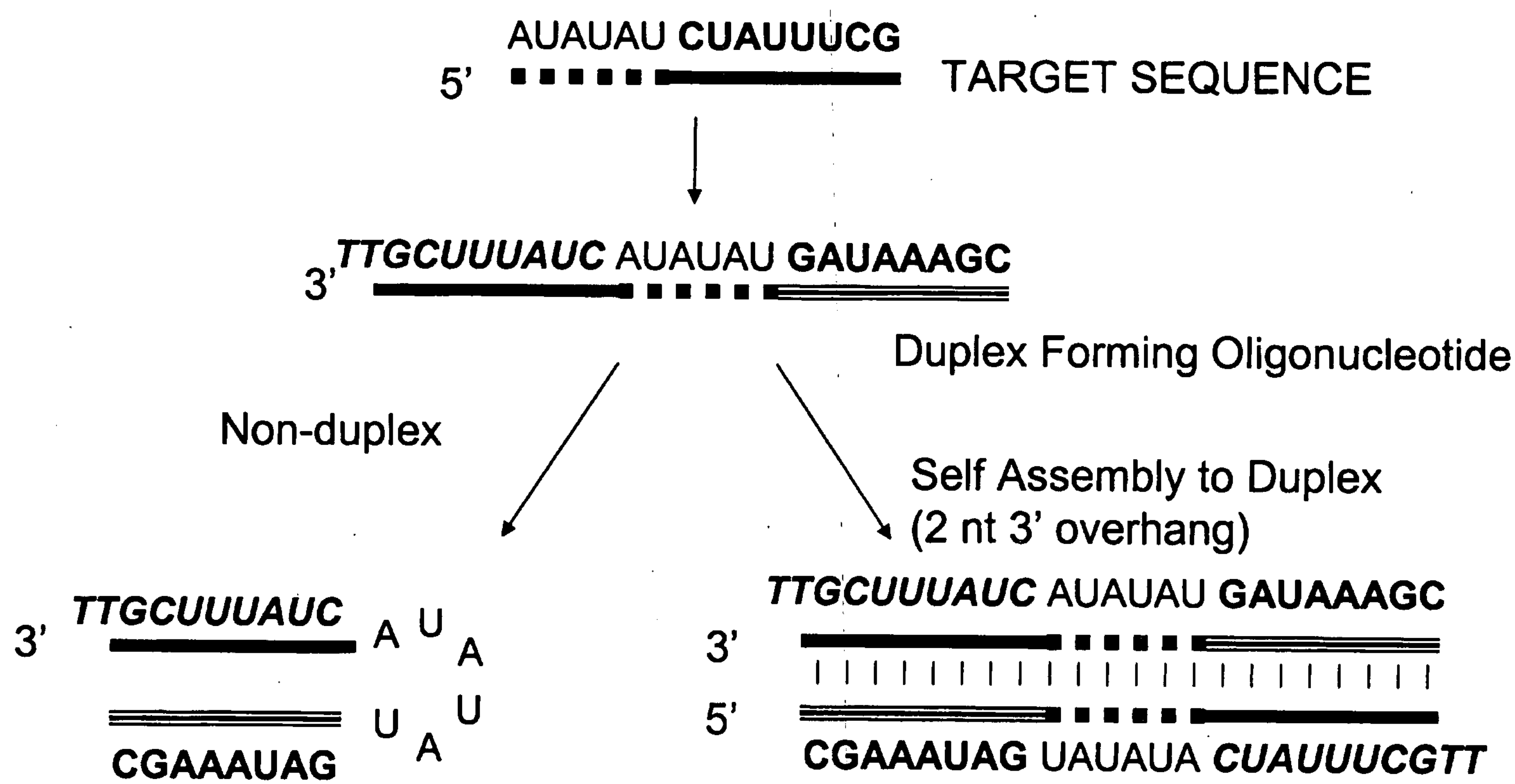


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition of Target Sequence Expression

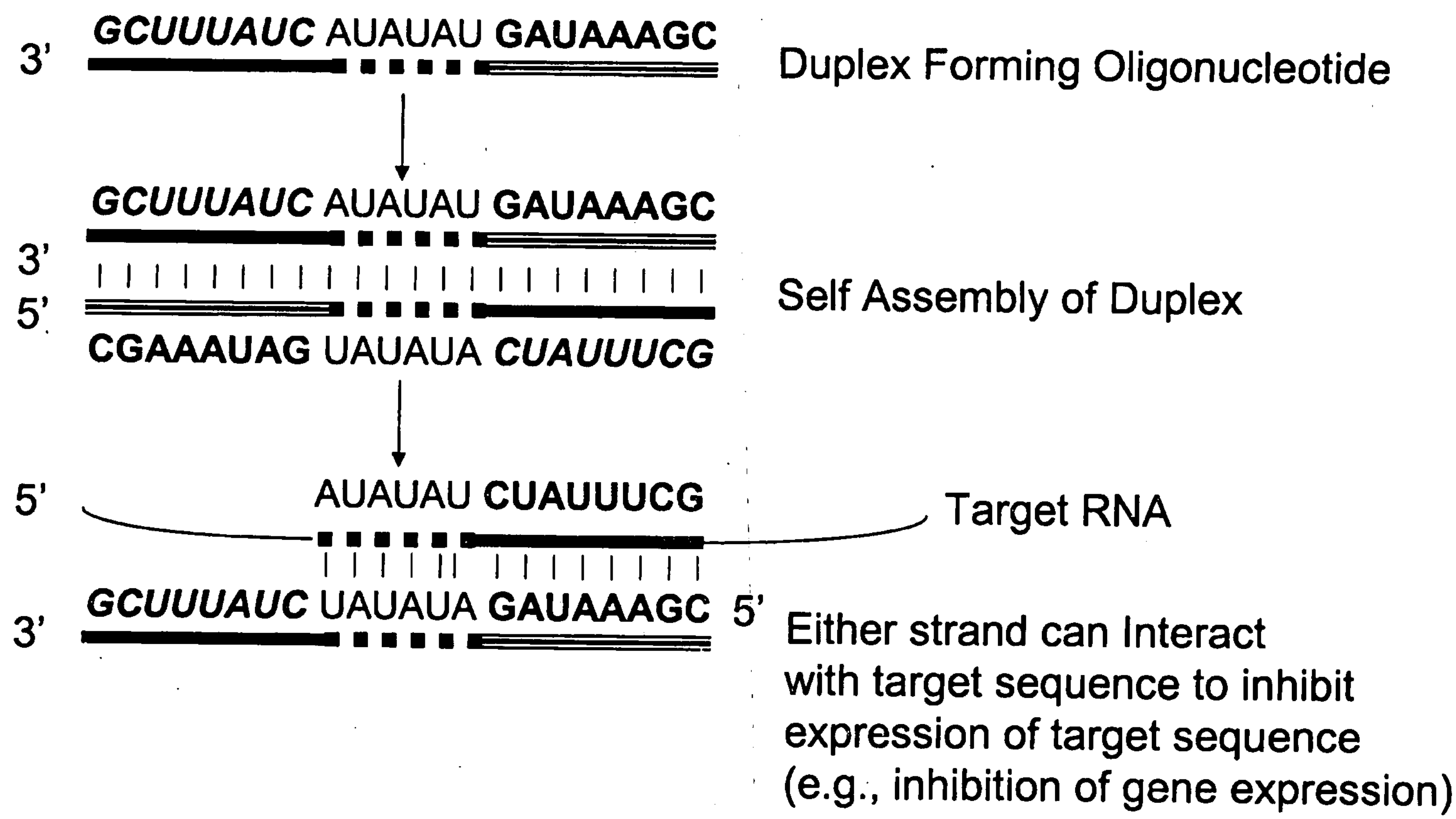
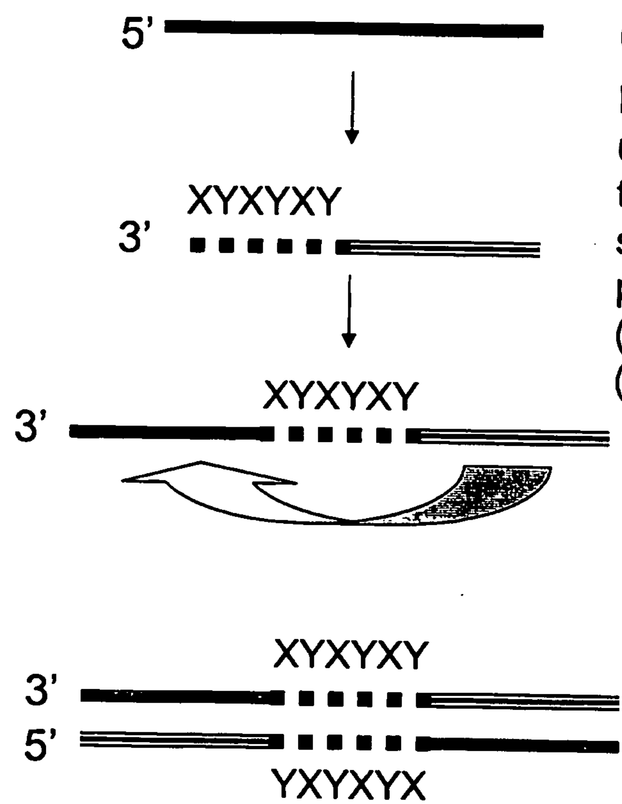


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences



Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length)

Design Complementary Sequence and utilize modified nucleotides (shown as X, Y) that interact with a portion of the target sequence and result in the formation of a palindrome/repeat sequence (e.g., 2 to 12 nucleotides) at 3'-end (dashed portion)

Append inverse sequence of Complementary region to 3'-end of palindrome/repeat sequence

Hybridize self complementary strands to form duplex siNA construct

Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions

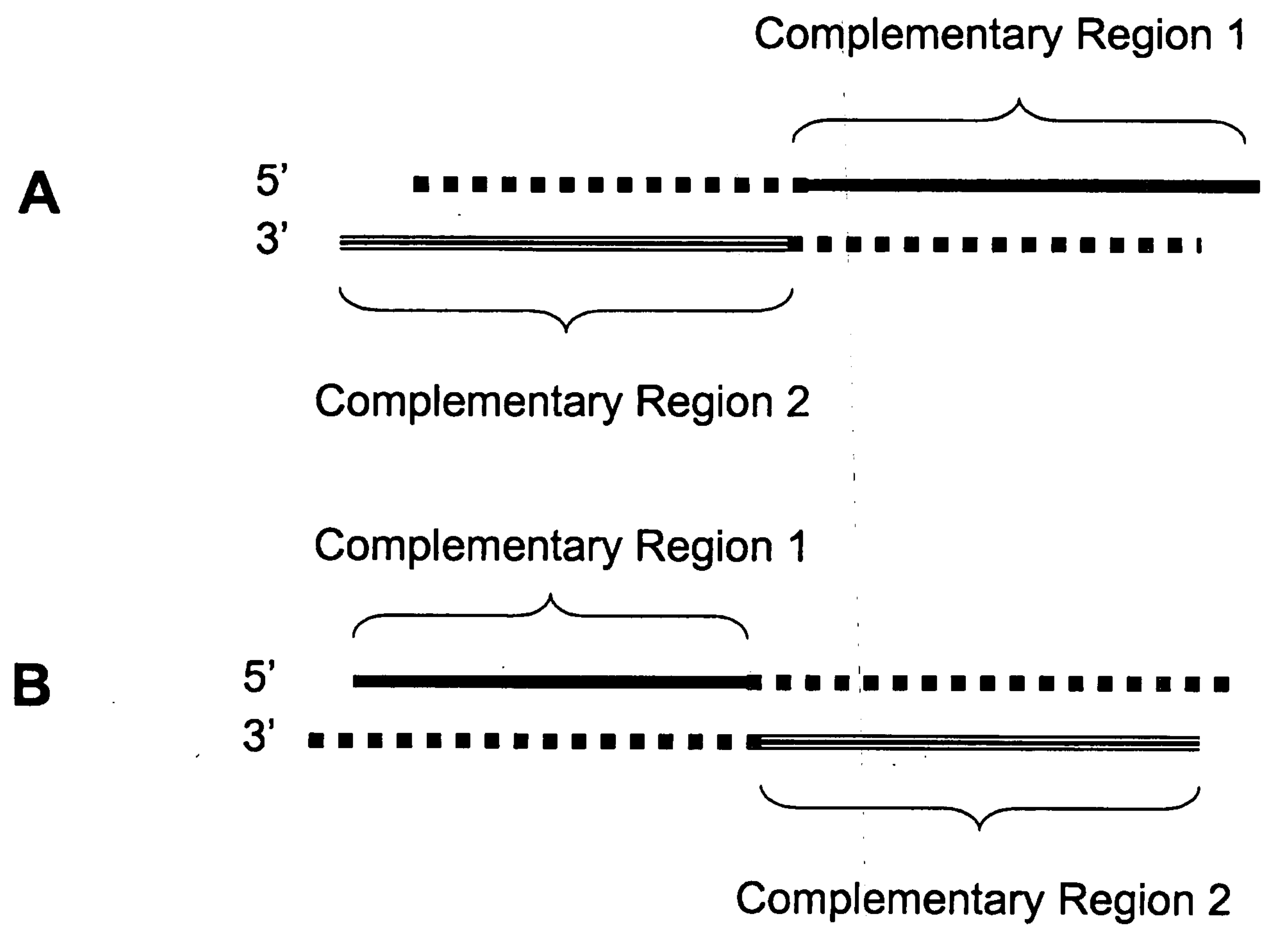


Figure 17: Examples of hairpin multifunctional siNA constructs with distinct complementary regions

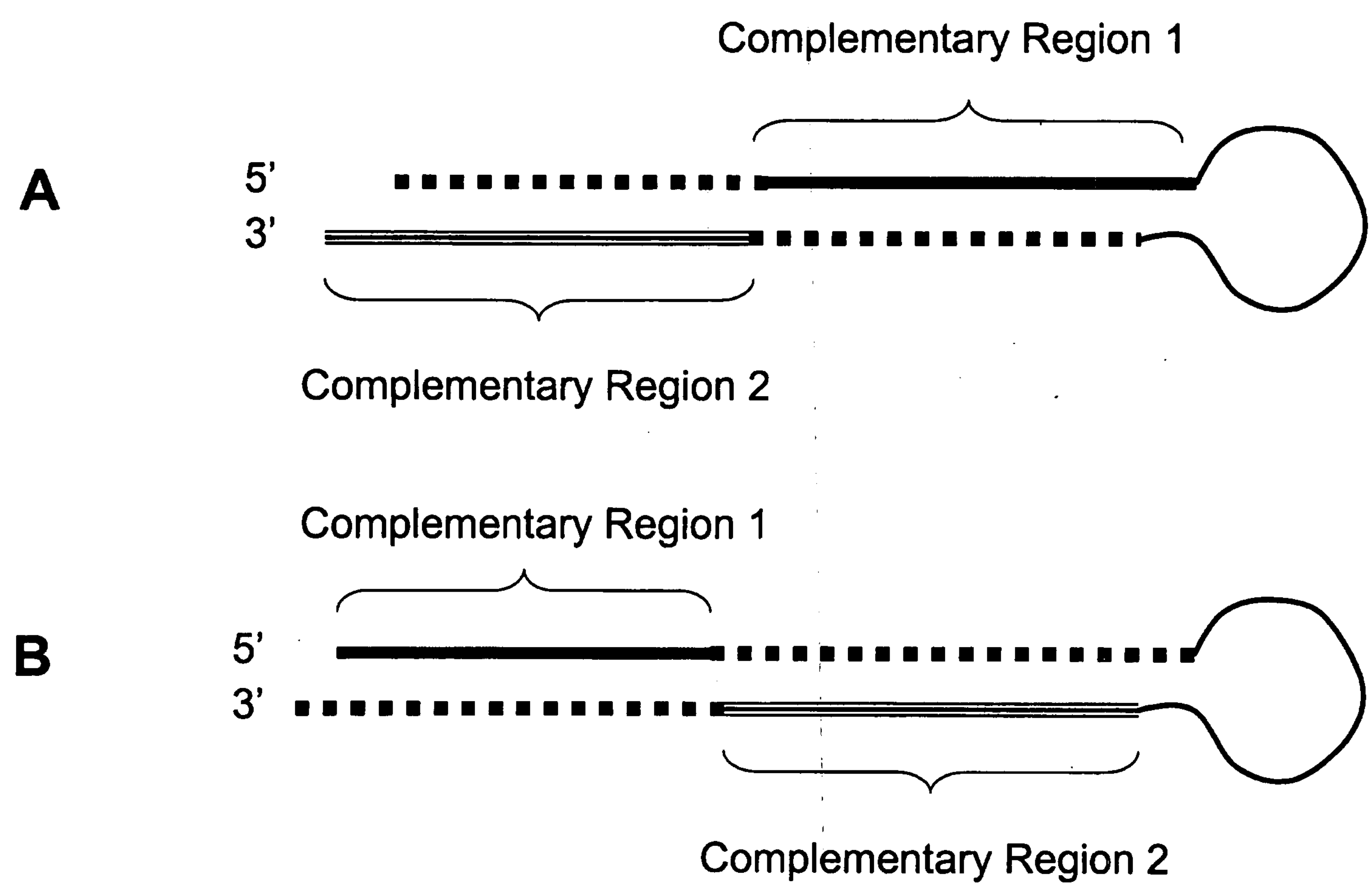


Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

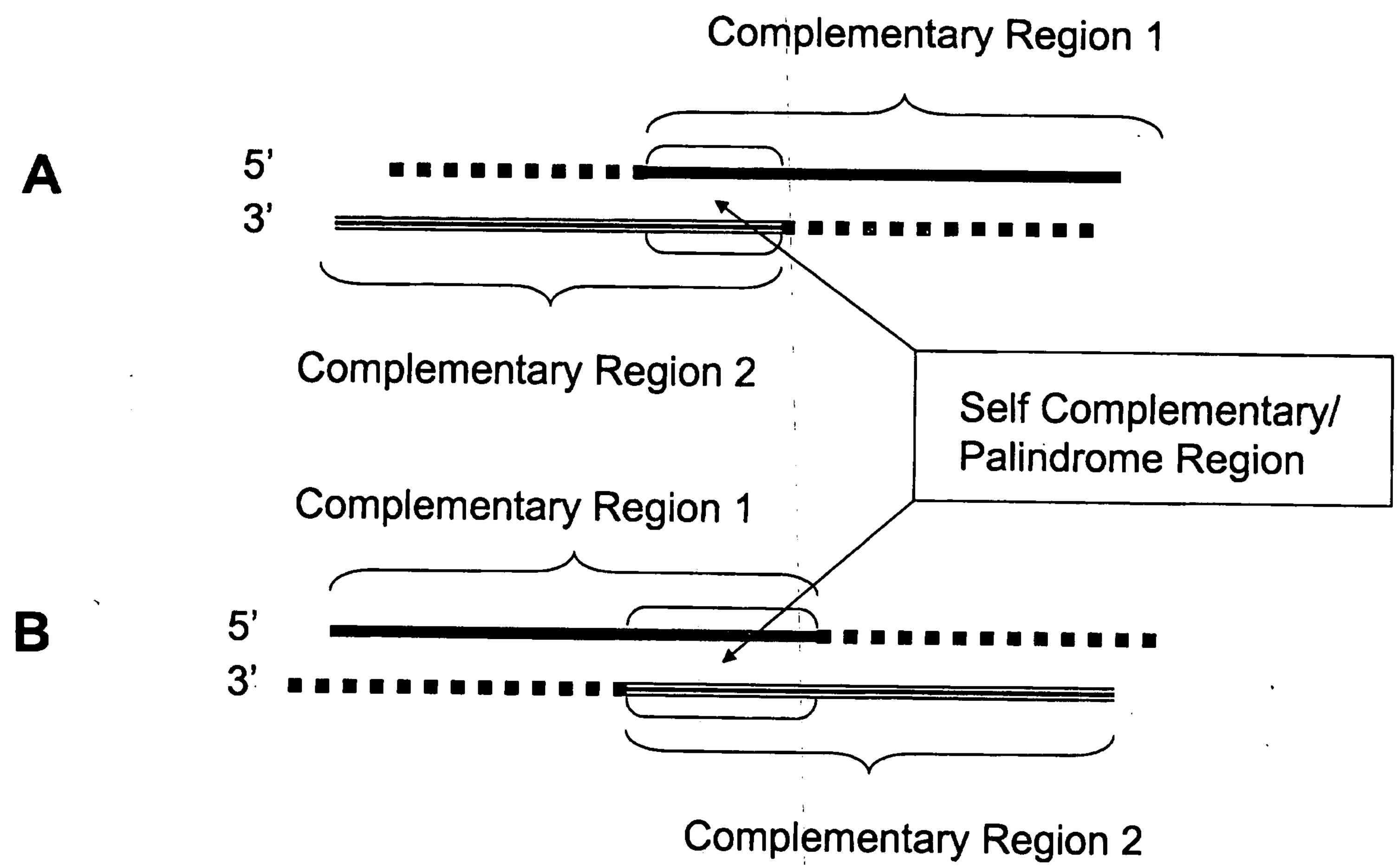


Figure 19: Examples of hairpin multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

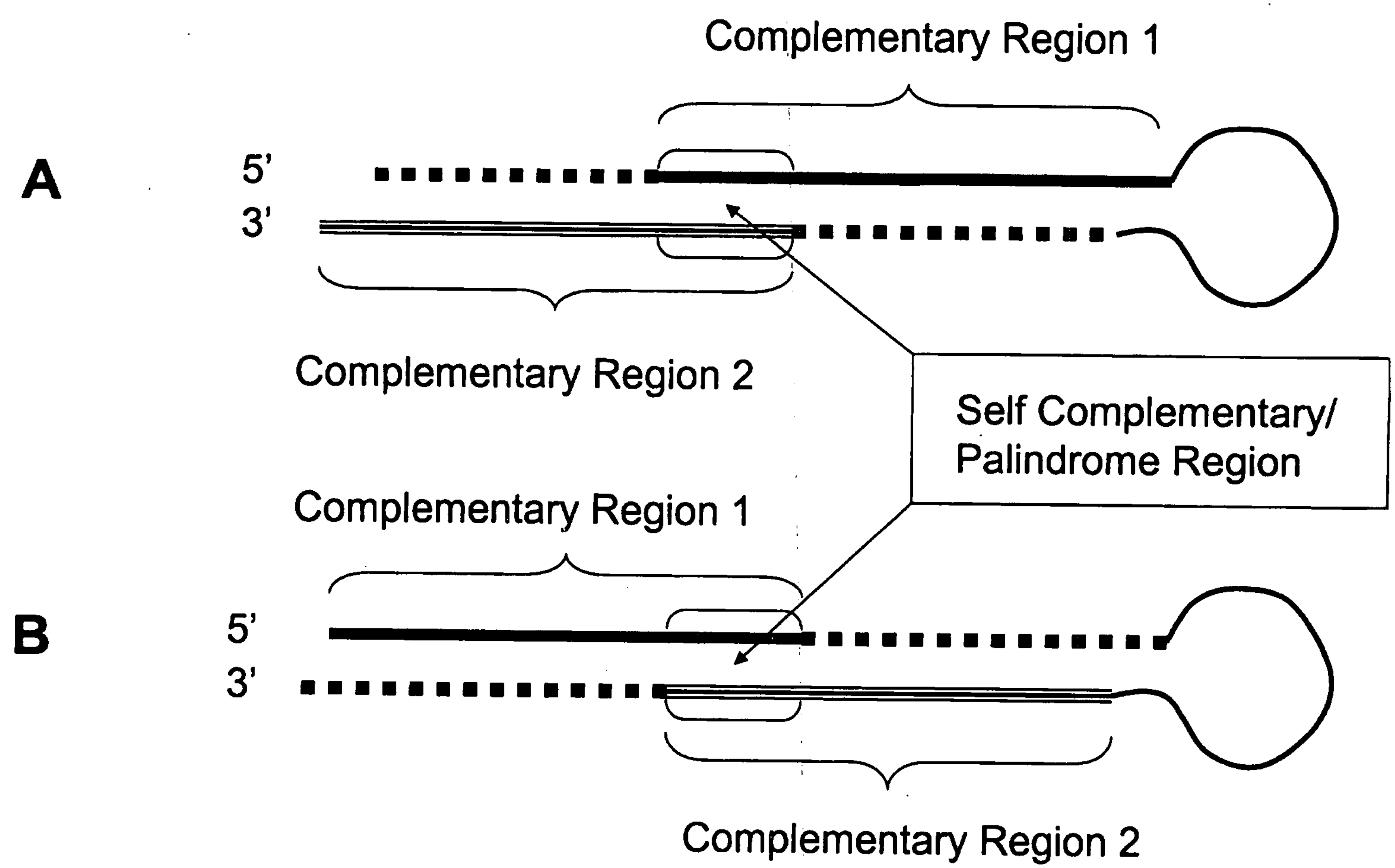


Figure 20: Example of multifunctional siNA targeting two separate Target nucleic acid sequences

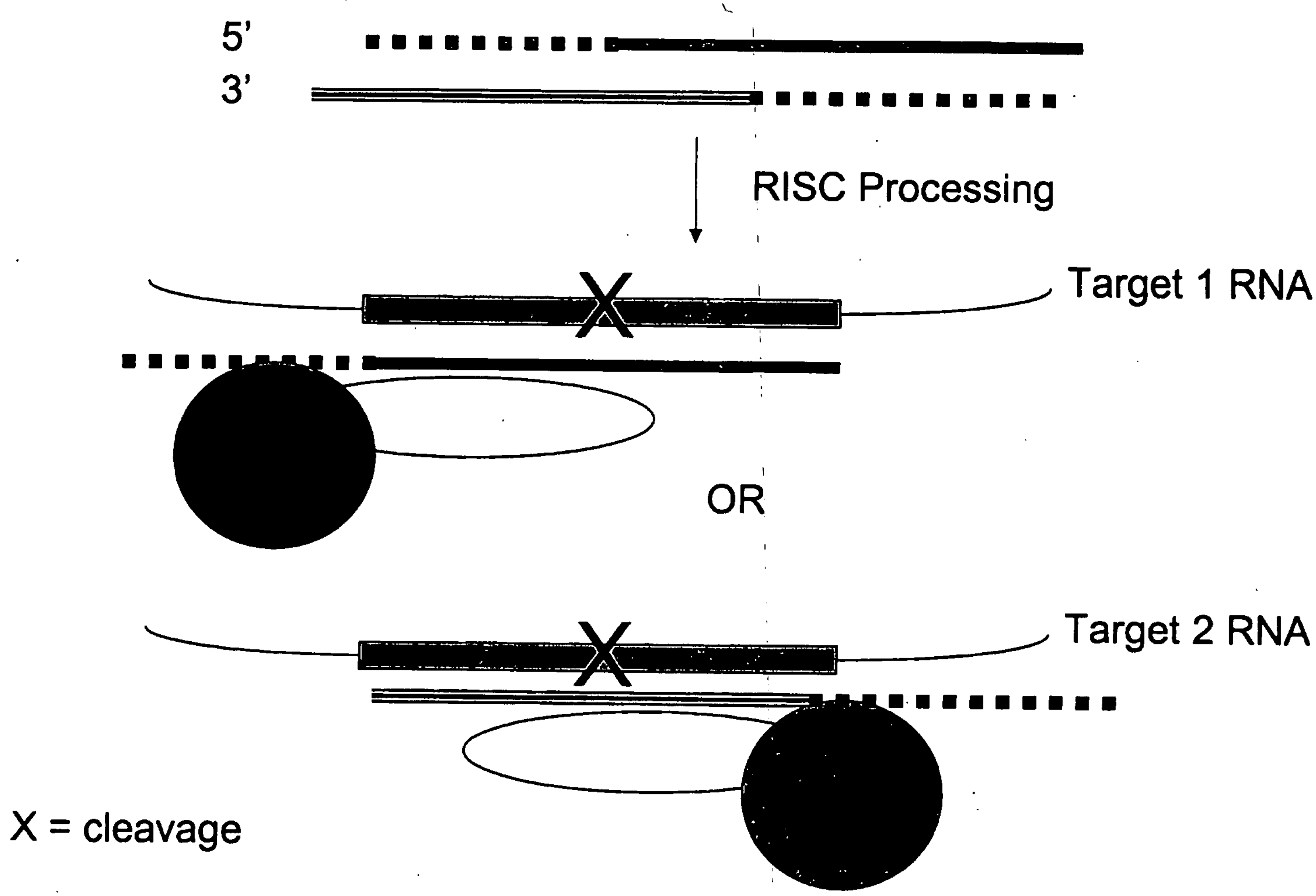


Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence